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2017 Scientific Abstract Book

1. Diagnostic Value of PLAG1 Assessment in Lipoblastomas and Pediatric Lipomatous Tumors: Comparison of PLAG1 FISH and Immunohistochemistry.

O Lopez Nunez*[1]*, R Alaggio*[2]*, S Ranganathan*[2]*, L Schmitt*[3]*, J Picarsic*[2]*; [1]University of Pittsburgh Medical Center, Department of Pathology, Pittsburgh, Pennsylvania; [2]Children's Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [3]Children's Hospital of UPMC, Pittsburgh, Pennsylvania

Background: Lipoblastomas (LB) are benign pediatric neoplasms thought to arise from lipoblasts. Up to 70% show PLAG1 (8q12) rearrangements, whereas 18% are associated with polysomy 8. Up to 10% have been identified in young adult patients and may be difficult to distinguish from myxoid liposarcomas or from well differentiated liposarcoma. The Interphase Fluorescent In-Situ Hybridization (FISH) analysis with a commercial PLAG1 break-apart probe is a new ancillary diagnostic test for the confirmation of LBs (PLAG-FISH). The aim of this study is to assess the diagnostic utility of PLAG1 protein expression with immunohistochemistry (PLAG-IHC), as compared to PLAG-FISH in a series of pediatric lipomatous tumors.

Methods: 34 benign pediatric lipomatous tumors were analyzed with PLAG-FISH and PLAG-IHC. Original diagnoses included 23 Lipoblastomas and 11 lipomas (with and without thick fibrous septa). Cases were retrieved from the pathology files under IRB approval. LB cases were subtyped as myxoid, classic, maturing/lipoma-like, with one recurrence, while four lipomas were re-classified as maturing/lipoma LB. Formalin fixed paraffin-embedded tissue (FFPE) was utilized for prospective comparison of PLAG-FISH and PLAG-IHC. The immunoreactivity was graded per the percentage of positive nuclei (0 negative; <10% 1+, 10%-50% 2+, >50%; 3+; positive control: LB with +cytogenetics). PLAG1-FISH was considered positive if PLAG1 break-apart signal was present in ≥10% of cells (positive control: salivary gland tumor).

Results: LBs included myxoid (n=3), classic (n=9), maturing/lipoma-like (n=14) subtypes, and one relapse with predominant spindle cell morphology. The overall median age for re-classified LB was 3 years with myxoid and classical subtype, 3 y (range: 0.7-14 y), maturing/lipoma-like subtype, 5.5 y (range: 0.5-13 y); and lipomas, 6 y (range: 1-12 y). PLAG-FISH was positive in 38% (6/16) LB, which was limited to myxoid, classical subtypes and the relapsed case (Table). PLAG-IHC (2-3+) was present in 41% (11/27) LB with nuclear staining in small primitive cells and spindled cells of fibrous septa, but less staining in adipocyte nuclei. PLAG-IHC 2-3+ protein expression was present in a higher percentage of the myxoid (66%) and classic (56%) subtypes, as compared to maturing/lipoma-like (21%) subtype. None of the lipomas were positive for PLAG-FISH or IHC (2-3+) (Table).

Table. PLAG-IHC and FISH results in LB and Pediatric Lipomatous tumors.

Re-classified	IHC pattern	IHC (n)	FISH + (n)	FISH - (n)	FISH failed (n)
LB myxoid n=3	**0**				
	1	1	1		
	2-3	2	1	1	0
LB classic n=9	**0**	2	1		1
	1	2		1	1
	2-3	5	2		3
LB maturing/lipoma like n=14	**0**	10		5	5
	1	1		1	
	2-3	3		2	1
LB relapse n=1	**0**				
	1				
	2-3	1	1		
Lipoma with thick fibrous septa n=2	**0**	2		1	1
	1				
	2-3				
Lipoma with minimal to no fibrous septa n=4	**0**	3		3	
	1	1		1	
	2-3				
Lipoma with hibernoma like features n=1	**0**	1		1	
	1				
	2-3				

Conclusion: PLAG1 expression in LBs is a sensitive marker of 8q12 rearrangement in LB with myxoid and classic morphology and can be used as a screening marker, obviating the need for FISH analysis if 2-3+ staining is present. PLAG-IHC staining of spindled cells in the thick fibrous septa deserves further investigation. Also the so-called maturing/lipoma-like subtype may be considered distinct from LB with classic/myxoid morphology but further studies are needed.

2. **Age-Specific Effects of Common Genetic Variants and Human Leukocyte Antigen Types**

***J Goldstein**, L Bastarache, S Van Driest, J Denny, D Aronoff;* Vanderbilt University Medical Center, Nashville, Tennessee

Background: Patient cohorts defined by the electronic health record (EHR) enable the study of a broad range of phenotypes collected as part of routine clinical care in diverse patient populations. Genome-wide association studies (GWAS) and phenome-wide association studies (PheWAS) using EHR cohorts have successfully replicated the findings of many disease-specific observational studies.

Prior PheWAS studies have treated age as a linear covariate with two age strata – pediatric and adult. However, specific diagnoses are often restricted to narrow age groups or due to disparate pathologic mechanisms in different age groups. We performed PheWAS using finer age brackets that are developmentally and biologically motivated to identify novel SNP:disease associations across age strata.

Methods: We divided our cohort of 37,380 patients with longitudinal EHR and genotyping data on the Illumina Infinium

Human Exome Bead Chip based on the patient's age at the time of diagnosis into age <1, 1-4, 5-8, 9-13, 14-21, 22-35, and 36-60 years. We identified cases and controls using ICD9/10 billing codes. Cases are defined as patients with a diagnosis coded at an age in the age range of interest. We imputed HLA types based on SNPs in the HLA region. We performed logistic regression for the presence of the disease using SNP, age, and sex as variables.

Results: We used rs213950, a *CFTR* variant in linkage disequilibrium with the ΔF508 mutation, as a positive control. As expected, this variant was consistently associated with cystic fibrosis. Analyzing by age shows the expected progression of cystic fibrosis with pneumonia in early childhood followed by later development of bronchiectasis and secondary diabetes mellitus. We tested SNPs with known associations in adults. rs157580 in *TOMM40* is known to be associated with a decreased risk of hyperlipidemia in adults (P=7.0E-5, odds ratio [OR]=0.879). We identified a new association with an increased risk of asthma exacerbation in ages 5-8 and 22-35 (Age 5-8 P=6.2E-5, OR=2.122). We also tested HLA-associations. HLA-C-0701 is known to be associated with an increased risk of Type I diabetes (best P=3.0E-6, best OR=2.73). We identified a new association with reduced risk of gastroesophageal reflux disease (GERD) and esophagitis in infants and children (infant P=2.2E-6, OR=0.503).

Conclusion: This study identified novel SNP:disease associations in infants and young age groups. Use of narrow age groups allows for better study of diseases with different peak incidences.

3. TERT Overexpression in Neuroblastoma

A Nael*[1]*, R Matsuno*[1]*, J Shows*[1]*, M Warren*[1]*, J Gastier-Foster*[2]*, N Ikegaki*[3]*, H Shimada*[1]*;

[1]Children's Hospital Los Angeles, Los Angeles, California; [2]Nationwide Children's Hospital, Columbus, Ohio; [3]University of Illinois at Chicago, Chicago, Illinois

Background: Peripheral neuroblastic tumors (pNTs) are known to offer one of the best models for analyzing biologically significant relationships between genomic/molecular properties and morphological manifestations. Historically, International Neuroblastoma Pathology Classification [INPC, Favorable Histology (FH) vs. Unfavorable Histology (UH)] and *MYCN* oncogene status (non-amplified vs. amplified), along with other genomic/molecular alterations, have been used for predicting clinical outcomes of this disease. Recently we reported highly aggressive behavior of MYC family-driven neuroblastomas, defined by augmented expression of either MYCN protein (significantly associated with *MYCN* amplification) or MYC (aka C-myc) protein (not associated with *MYCN* amplification) and comprising more than 50% of UH pNTs. However, there is a considerable number of UH pNTs whose molecular alterations are yet to be defined. We have been interested in telomere lengthening mechanisms providing neuroblastoma cells with infinite proliferating capability. In our previous study, we reported that loss of ATRX (a-thalassemia/mental retardation syndrome X-linked) protein expression, leading to alternative lengthening of telomere, was observed in older children with UH and non-MYC family-driven pNTs (2017 SPP Spring meeting). In this study, we report TERT (telomerase reverse transcriptase) expression in the same cohort of cases used in the ATRX study.

Methods: Immunohistochemical study detecting TERT expression was performed using a total of 100 neuroblastomas of undifferentiated (1), poorly differentiated (95), and differentiating (4) subtype from the file of Children's Oncology Group Neuroblastoma Pathology Reference Laboratory. All of these tumors were tested for ATRX protein expression in our previous study. The results [TERT overexpression (+) vs. non-overexpression (-)/(+/-)] were analyzed with age at diagnosis [<18 months (37), 18 months-5 years (26) and >5 years (37)], INPC [FH (19) and UH (81)], MYCN status [non-amplified (74), amplified (22) and not tested (4)] and MYCN/MYC protein expression [overexpression (25/24) and non-overexpression (75/76)].

Results: 39 tumors demonstrated TERT(+). They were distributed in all age groups: 17 (45%) in <18 months, 7 (27%) in 18 months–5 years, and 15 (39%) in >5 years. 24 (62%) TERT(+) tumors were associated with MYCN/MYC protein overexpression. While 15 (38%) TERT(+) tumors did not have MYCN/MYC overexpression, and 14 of them were UH. In this series, only one tumor had TERT(+) and loss of ATRX expression.
Conclusion: In contrast to loss of ATRX, TERT overexpression was observed in all age groups and in both MYC family-driven and non-MYC family-driven pNTs. The vast majority of TERT(+) and non-MYC family-driven pNTs had UH. TERT overexpression, similar to ATRX loss, seemed to be associated with unique subgroup in the UH pNTs, where proliferating neuroblasts could be resistant to replication senescence/cell death due to telomere erosion.

4. The Jumonji-domain histone demethylase inhibitor JIB-04 deregulates oncogenic programs in Ewing Sarcoma, resulting in impaired cell and tumor growth.
***P Jedlicka**, J Parrish, M Sechler, T McCann, L Martin Sobral, W Ren, K Jones, A Tan;*
University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado
Background: Ewing Sarcoma is an aggressive malignant neoplasm of bone and soft tissue affecting children and young adults. Ewing Sarcoma is driven by transcription factor fusion oncoproteins, most commonly EWS/Fli1. While some patients can be cured with high-dose, multi-agent, chemotherapy, those that cannot currently have few options. Targeting of the driver oncofusion remains a logical therapeutic approach, but has proven difficult. Recent work has pointed to epigenetic mechanisms as key players, and potential new therapeutic targets, in Ewing Sarcoma. Having previously implicated a Jumonji-domain histone demethylase (JHDM) in the biology of Ewing Sarcoma, in this study we examined the activity of the JHDM pharmacologic inhibitor JIB-04 in this disease.
Methods: Effects of JIB-04 on Ewing Sarcoma growth were evaluated using a panel of validated, patient-derived Ewing Sarcoma cell lines, in vitro cell growth and colony formation assays, a tumor xenograft model, and assays of cell proliferation and survival, and DNA damage. Global gene expression profiling using next generation RNA sequencing and bioinformatic analysis were performed to understand JIB-04 effects on the Ewing Sarcoma transcriptome. Quantitative reverse transcription followed by polymerase chain reaction (qRT-PCR), chromatin immunoprecipitation (ChIP) followed by qPCR, and immunoblotting were performed to understand candidate mechanisms of drug action.
Results: We show that JIB-04 impairs proliferation and survival of Ewing Sarcoma cells in vitro, and that orally dosed JIB-04 inhibits the growth of xenograft tumors in vivo. Mechanistic studies reveal increased H3K4 methylation and concomitant induction of growth suppressive genes, including CDKN1A, as candidate mechanisms of drug action. These changes are accompanied by downregulation of many growth and tumor promoting genes, including members of the homeobox B and D families. Among genes altered in expression are a number of genes previously implicated in Ewing Sarcoma pathogenesis, and gene set enrichment analysis reveals that JIB-04 dramatically alters the global EWS/Fli1 signature. This results in predominant opposition of EWS/Fli1 effects, including downregulation of pro-proliferative pathways normally under positive control by the oncofusion. Consistent with known non-transcriptional functions of JHDMs or/and global transcriptional stress, we also observe an increase in DNA damage upon JIB-04 treatment of Ewing Sarcoma cells.
Conclusion: Our studies are the first to demonstrate activity of a JHDM pharmacologic inhibitor in Ewing Sarcoma, and identify multiple disease-relevant mechanisms of drug action.

5. Hashimoto thyroiditis is differentially associated with variants of pediatric papillary thyroid carcinoma and correlates with better prognosis

***H Wang**, H Correa, M Sanders, J Liang;* Vanderbilt University Medical Center, Nashville, Tennessee

Background: The association between Hashimoto thyroiditis (HT) and papillary thyroid carcinoma (PTC) has long been debated and yet remains controversial. Most if not all studies examining such association were based on adult or general population, while a systematic analysis in the pediatric group has not been reported. The association between HT and individual variants of PTC is unclear.

Methods: To evaluate the incidence of HT in pediatric PTC, we retrospectively analyzed the demographic, serologic and clinicopathologic characteristics of all patients aged 21 or younger who underwent thyroidectomy and were diagnosed with PTC at our institution from 2005 to 2017. To control for possible confounding effects, all pediatric patients with matched demographic characteristics who were diagnosed with non-PTC primary thyroid neoplasm during the same period at our institution were assembled as a control group for comparison of HT incidence. HT was defined by the presence of diffuse lymphocytic thyroiditis in surgical resection specimens in combination with either an established clinical diagnosis of HT or with elevated autoantibodies to thyroglobulin and/or thyroid peroxidase. Cases with histologic evidence of lymphocytic thyroiditis but without available serologic data were excluded from the study.

Results: We identified 35 pediatric patients with PTC (F:M 4.8; age 10-20, mean 14.2 years), including 22 classic, 6 follicular, 5 diffuse sclerosing, 1 solid and 1 cribriform-morular variant. The control group comprised 29 patients with non-PTC primary thyroid neoplasm (F:M 2.2; age 9-18, mean 14.9 years), including 24 follicular adenoma, 3 follicular carcinoma and 2 poorly differentiated carcinoma. Patients with medullary thyroid carcinoma were excluded due to unmatched demographic characteristics with younger age and a male predominance. Children with PTC showed a significantly higher incidence of HT compared to control (40.0% vs 6.9%, p = 0.0031) and to an adult PTC group (n=11155) pooled in a recent meta-analysis by Resende de Paiva, C et al. (18.9%, p = 0.0015). Among the variants of PTC in children, diffuse sclerosing variant exhibited the strongest association with HT (80.0%, p = 0.0015), followed by classic variant (40.9%, p = 0.0054). In contrast, none of the 6 patients with follicular variant of PTC had co-existing HT. Children with classic PTC and co-existing HT exhibited lower prevalence of extrathyroidal extension and lower tumor stages compared to patients with classic PTC alone. The incidences of advanced nodal stage (N1b) and persistence of disease after radioiodine therapy were also significantly lower (p= 0.0115 and 0.0294, respectively).

Conclusion: HT is significantly associated with PTC in pediatric patients with a higher incidence compared to adults. The association of HT with pediatric PTC is subtype-dependent, with diffuse sclerosing variant having the highest incidence while follicular variant the lowest. In children with classic PTC, HT is associated with better prognosis.

6. Thyroid transcription factor-1 (TTF-1) immunohistochemistry helps distinguish type 1 congenital pulmonary airway malformations (CPAMs) from other congenital cystic lung lesions

***H Huang**, L Parsons, J Jarzembowski;* Medical College of Wisconsin, Milwaukee, Wisconsin

Background: Congenital pulmonary airway malformations (CPAMs) are developmental lung anomalies presumed to result from airway obstruction *in utero*. Although there is currently much discussion as to the best categorization of these lesions, the Stocker classification remains the most widely utilized. Clinical and pathologic characteristics may overlap between CPAM type 1 (T1) and type 2 (T2), as well as other cystic lung lesions, presenting a diagnostic challenge. Thyroid transcription factor 1 (TTF1)

regulates, among other things, lung-specific genes and is important to pulmonary morphogenesis; mutations have been associated with cystic lung disease. We therefore sought to determine whether immunohistochemical (IHC) expression of TTF1 would be altered in CPAMs or other cystic lung lesions.

Methods: Following IRB approval a search of the surgical pathology database between 1985 and 2017 was performed for cases diagnosed as CPAM/CCAM, sequestration, bronchogenic or foregut cyst, or congenital lobar emphysema. Cyst size(s) was obtained from original surgical pathology gross reports. H&E slides from each case were reviewed for diagnostic confirmation, and representative tissue blocks were selected. TTF1 IHC was performed per manufacturer protocol. TTF1 stained slides were scored for staining intensity and distribution within the cyst lining cells, and the expression product was calculated as intensity x distribution. Age, sex, and coexisting conditions were collected from the electronic medical record. Expression patterns of subgroups were compared by Student t-tests and correlation coefficients were calculated for relationships between expression and clinical data.

Results: We identified and stained 13 CPAM T1, 28 CPAM T2, 10 congenital lobar emphysema cases, 10 sequestrations, and 2 bronchogenic cysts. All lesions except T1s showed uniform strong TTF1 expression in cyst lining cells. TTF1 staining patterns in CPAM T1 mirrored the TTF staining pattern observed in native bronchi, which was less uniform and weaker than the staining of the lining cells of CPAM T2 as measured by mean intensity (2.19 for T1 vs 2.88 for T2; p=0.0008), mean distribution (2.38 vs 2.91; p=0.0019), and expression product (5.68 vs 8.48; p = 0.0004). As expected, T1s had larger cysts and were diagnosed in older children than T2s.

Conclusion: We found that TTF1 IHC staining differs in the cyst lining cells of T1 CPAM and T2 CPAM, suggesting that this may be a useful adjunct in differentiating between these two lesions. The fact that TTF1 expression in T1 CPAM generally mimics the pattern observed in larger bronchi supports the notion that this malformation may be derived from more proximal lung elements than T2 CPAMs and may distinguish it from other cystic lung lesions of childhood.

7. The Pattern of Distribution of Eosinophils in the Pediatric Colon is Superior than the Total Number of Eosinophils in Predicting Disease in Patients with Mild Mucosal Eosinophilia

Bernieh*[1]*, A Saad*[2]*; [1]University of Mississippi Medical Center, Jackson, Mississippi; [2]UMMC and Baptist Health Medical Center, Jacksonville FL, Jackson, Mississippi

Background: The significance of mild mucosal eosinophilia in an otherwise normal colonic mucosa in children remains poorly defined and, when present, raises significant confusion as to how to manage these patients.

Methods: To evaluate the significance of mild mucosal eosinophilia in children, we conducted a retrospective study of all children (1-18 years-old) from 1985 to 2015. Inclusion criteria were: Patients with biopsies from all five parts of the colon (cecum, ascending, transverse, descending, and rectosigmoid), follow-up of at least 1.5 years, and mild mucosal eosinophilia in otherwise normal colonic biopsies. Eosinophils were evaluated for number (by counting 5 areas with the highest number of eosinophils), distribution (within the surface or crypt epithelium), and clustering (defined as a cluster of ≥5 eosinophils).

Results: The search yielded 66 patients (36 males and 30 females; mean age 8.1 years; range 2.1-17.6 years). On followed up, 28 patients were diagnosed with food allergy, 23 patients with inflammatory bowel disease (IBD), 10 patients with parasitic infection, and 5 patients with eosinophilic gastroenteritis (EGE). No specific etiology was identified in 13 patients. No difference in the total number of eosinophils existed between all patient groups. All patients who developed disease showed increased number of intraepithelial forms compared to those who did not (*P*=0.0001). The

highest number of intraepithelial forms was noted in patients with IBD and EGE (12 ± 1.9 and 8.3 ± 1.5 eosinophils/hpf, respectively), followed by those who developed parasitic infection (5.3 ± 0.9 eosinophils/hpf), and food allergy (3.4 ± 0.6 eosinophils/hpf). Patients who developed disease showed increased number of clusters compared to those who did not (*P*=0.00003). The highest number of clusters was observed in patients who developed EGE (5 ± 1 clusters/hpf) followed by IBD (4 ± 1.1 clusters/hpf), parasitic infection (3.7 ± 0.9 clusters/hpf), and food allergy (2.9 ± 0.4 clusters/hpf).

Conclusion: We conclude that, in children with mild colonic mucosal eosinophilia, the pattern of distribution (intraepithelial location and presence of clusters), and not the number of eosinophils correlates with the likelihood of developing a disease. Colonic mucosa of patients with mild mucosal eosinophilia should be evaluated for intraepithelial eosinophils and eosinophils clusters.

8. Liver biopsy immunohistochemical detection of lipid peroxidation, sinusoidal stellate cell activation, cell proliferation, and hepatocyte apoptosis in pediatric nonalcoholic fatty liver disease: a pilot study of relationship with metabolic syndrome.

***J Wang**, N Ellington, C Ramirez, D Rakheja, D Zwick;* UT Southwestern Medical Center / Children's Health, Dallas, Texas

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children. The histologic spectrum of disease ranges from steatosis to nonalcoholic steatohepatitis, which may lead to fibrosis and cirrhosis. NAFLD activity scores (NAS) are too insensitive for detection of early changes in disease activity or early responses to therapy. The aims of this study are to investigate the relationship of NAFLD severity, as determined by presence or absence of metabolic syndrome, with expression of IHC markers of oxidative stress (malondialdehyde [MDA]), hepatic stellate cell activation (alpha-smooth muscle actin [SMA]), hepatocyte apoptosis (caspase cleaved cytokeratin 18 [ccCK18]), and cell proliferation (Ki-67), and determine the interobserver variability of interpretation of these markers.

Methods: Liver biopsies from 14 pediatric patients with NAFLD, with and without metabolic syndrome at the time of biopsy, were stained with SMA, MDA, Ki-67, and ccCK18. A grading system was devised for measuring IHC expression in lobules and portal tracts (PT). Stains, NAS, and fibrosis stage were independently evaluated/determined by 3 blinded pediatric pathologists. Interobserver agreement was measured for categorical variables using weighted Cohen kappa scores and for nominal variables using correlation coefficients. Mean scores from the 3 observers for each IHC parameter were calculated and differences between expressions in subjects with or without metabolic syndrome were determined using Student's t-test.

Results: There were 9 subjects with and 4 without metabolic syndrome; 1 subject lacked steatosis and was excluded from correlation with clinical data. There was moderate to substantial interobserver agreement for SMA grade and intensity and hepatocellular MDA grade (k=0.40-0.86). Interobserver correlations for Ki-67 cell density, MDA positive macrophages, and ccCK18 positivity were all significant ($p<0.05$ to <0.001). The interobserver agreement for NAS components ranged from slight to near perfect (k=0.19-0.92). Hepatocyte ballooning showed the lowest interobserver agreement (k=0.19-0.3). There was significant direct correlation of PT SMA grade, PT Ki-67 positive cell density, PT NAS inflammation, and composite NAS score (p=0.002-0.05) and significant indirect correlation of hepatocellular MDA grade ($p<0.01$) with metabolic syndrome status.

Conclusion: Significant correlations between selected IHC markers of oxidative stress, stellate cell activation, hepatocyte apoptosis, and cell proliferation with metabolic syndrome indicate that these markers are reliable indicators of NAFLD disease severity. Interobserver variability is better than those

observed with NAS. The utility of these IHC markers for monitoring disease activity and treatment response is subject to further study.

9. **Cytokeratin 7-Positive Intermediate Hepatocytes Are Absent to Rare in Pediatric Non-Alcoholic Fatty Liver Disease Biopsies**

***S Logan**, S Caltharp, H Rytting;* Children's Healthcare of Atlanta, Atlanta, Georgia

Background: The hepatic repair response includes increased hepatic progenitor cells (HPC), ductular reaction (DR), and increased intermediate hepatocytes (IH). The response pattern varies according to the type of liver injury and not all 3 components may be present. Immunohistochemistry for cytokeratin 7 (CK7) stains the 3 components. HPC are small darkly-stained single cells in the periportal region near the canals of Hering. The DR includes periportal strings and small clusters of darkly-stained cells. IH have normal hepatocyte morphology with light CK7 cytoplasmic staining and are common in cholestatic diseases. One recent paper suggests the presence of IH in transplant liver biopsies can help identify chronic ductopenic rejection. While studies have documented increased HPC and DR in pediatric non-alcoholic fatty liver disease (NAFLD), there is little documentation of IH. This retrospective pilot study examined the repair response including CK7-positive IH in pediatric NAFLD biopsies.

Methods: Twenty clinically-diagnosed pediatric NAFLD biopsies were sequentially identified from the 2015-2016 pathology files. Each biopsy was stained by immunohistochemistry for CK7. Three observers independently reviewed the CK7 stains for HPC, DR, and CK7 immunoreactive IH. Subsequently, the same observers independently reviewed hematoxylin-eosin and trichrome stains for % steatosis (score 0-3), lobular inflammation (score 0-3), and portal fibrosis (stage 0-4) using the standard NAFLD scoring and staging system. The presence IH was compared to average NAFLD scores and stages.

Results: No biopsy had abundant IH. 8 of 20 cases had rare or few mostly periportal IH. The cases included one normal-appearing biopsy, one with intermediate to high activity (score 5/6), and two with focal bridging fibrosis (stage 2-3/4). The sixteen remaining had low to intermediate activity scores (1-4/6) and minimal to mild periportal fibrosis (stage 1/4). The normal-appearing biopsy had a normal CK7 pattern of duct staining with rare periportal HPC and no DR or IH. All other biopsies had increased HPC with DR, both of which were more prominent in the two biopsies with more advanced fibrosis. There was no difference in NAFLD activity scores, NAFLD stages or liver function tests between cases with and without IH.

Conclusion: The CK7 staining pattern of the repair response in pediatric NAFLD includes increased HPC with DR and rare or absent IH. This pattern is consistent with descriptions of increased portal fibrosis and ductular reaction occurring early and frequently in pediatric NAFLD as compared to adult NAFLD. Numerous CK7 positive IH may in fact be fairly specific to cholestatic disease with interlobular duct damage, absence, or loss, as in chronic ductopenic rejection.

10. Comparison of cerebrospinal fluid cytology and neuraxis imaging in detection of leptomeningeal metastasis in patients with medulloblastoma

***H Wang**, A Kovach, A Coogan, J Liang;* Vanderbilt University Medical Center, Nashville, Tennessee

Background: Medulloblastoma is the most common malignant pediatric brain tumor and tends to disseminate in cerebrospinal fluid (CSF). Cytologic analysis of CSF and magnetic resonance imaging (MRI) of the neuraxis are two important modalities in assessment for leptomeningeal disease (LMD), which has implications for tumor staging, prognosis, and therapeutic approach. Studies examining the utilities of these two modalities in medulloblastoma have yielded conflicting conclusions.

Methods: To compare the abilities of cytology and imaging to detect LMD, we carried out a retrospective institutional review of CSF cytology and concurrent MRI imaging results from patients with medulloblastoma (1999-2016). CSF sampling location was noted. MRI findings from both brain and spinal cord performed within 30 days of CSF sampling were reviewed. Positive LMD was defined as positive or suspicious cytology, atypical cytology with positive or suspicious imaging, or normal cytology with positive or suspicious imaging confirmed by follow-up MRI. Sensitivity of cytology for LMD was calculated by comparing atypical, suspicious, and positive cases to negative cases, and sensitivity of imaging for LMD was calculated by comparing suspicious and positive cases to negative cases.

Results: We identified 160 CSF cytology samples with concurrent brain and spinal MRI from 43 patients (M:F 2.6; age 4-46, median 12 years). Cytology included 141 spinal (88%) and 19 intracranial (12%) samplings. Concordance between cytology and imaging findings was observed in 119 cases (74%); of these, 20 (17%) were positive and 99 (83%) were negative for LMD. Of the remaining 41 cases with cytology-imaging discordance (26%), 15 (37%) had abnormal cytology with negative imaging, and 26 (63%) had negative cytology with positive or suspicious imaging; follow-up MRI and/or tissue biopsy showed that 6 of the 26 cases with negative cytology and positive or suspicious imaging had been false positive MRI findings due to postoperative changes (n=3), resolving radiation effects (n=2), or meningioangiomatosis (n=1). The overall sensitivities for LMD was 62% by cytology and 77% by imaging. Among cytology samples, spinal CSF sampling showed higher sensitivity (75%), comparable to the sensitivity of imaging, and negative predictive value (92%) compared with intracranial sampling (31% sensitivity, 21% negative predictive value). LMD location did not appear to account for the low sensitivity of intracranial CSF, as 9 of 11 false negative intracranial samples had both intracranial and spinal imaging abnormalities.

Conclusion: Spinal CSF cytology and neuraxis MRI have comparable moderate sensitivity for detection of LMD in medulloblastoma. Intracranial CSF cytology appears to be an insensitive method, with a marked false negative rate in this small cohort. Our findings support recommendations to include both spinal CSF cytology and neuraxis MRI in evaluation of LMD in medulloblastoma.

11. Transcriptomic analysis for molecular subgrouping of former CNS-PNETs

N Willard*[1]*, A Donson*[2]*, N Foreman*[2]*, B DeMasters*[1]*; [1]University of Colorado, Aurora, Colorado; [2]Children's Hospital of Colorado, Aurora, Colorado

Background: Recently, DNA methylation studies (Sturm et al.) have suggested that embryonal tumors of the central nervous system (CNS), formerly designated CNS-primitive neuroectodermal tumors (CNS-PNETs) cluster into 4 distinct groups: high grade glioneuronal tumors (HGNET)-BCOR, HGNET-MN1, NB-FOXR2, and EFT-CIC, with embryonal tumors with multilayered rosettes, now ETMR-C19 altered, occupying a distinct 5th group further assessable by FISH or surrogate LIN28a immunohistochemistry. DNA methylation testing, however, is not yet widely available outside a few large research centers in North America or Europe. We hypothesized that the technique of RNA assessment by the more established, reproducible, widely-used transcriptomic analysis (microarray gene chips or RNAseq) might equally demonstrate this grouping and that these groups might correlate well with specific histopathological features. Namely we hypothesized that our previously diagnosed astroblastomas would cluster as HGNET-MN1 while ETMRs with true multilayered rosettes, abundant neuropil, and/or medulloepithelioma-like features would form a discrete group.

Methods: Re-interrogation of all pediatric tumors in our database for which we had Affymetrix microarray transcriptomic data that formerly carried the histological diagnosis of CNS-PNET, astroblastoma, or

ETMR/medulloepithelioma. ETMRs were further validated as C19-altered based on surrogate LIN28a IHC.

Results: 18 pediatric tumors meeting our inclusion criteria were identified with corresponding transcriptomic data. Signature transcripts for each subgroup that had been defined by Sturm et al correctly grouped all 5 astroblastoma-histology tumors as HGNET-MN1. All 5 ETMRs clustered tightly together and diagnoses were confirmed by immunopositive LIN28a IHC; 4 of the 5 ETMRs had been formerly diagnosed by the older nomenclature of medulloepithelioma (n=1) or embryonal tumor with abundant neuropil and true rosettes (n=3). 1 of 5, however even on histological review, remained a relatively patternless PNET-like small blue cell tumor without rosettes. LIN28a was focally positive, possibly due to tissue fixation issues, but this case tightly grouped with the other ETMRs by Affymetrix, which provided useful confirmation. Samples that grouped into EFT-CIC (n=1), NB-FOXR2 (n=3), and HGNET-BCOR (n=3) were less distinctive histologically.

Conclusion: Affymetrix is equally effective at subclassification of pediatric non-medulloblastoma/non-atypical teratoid/ rhabdoid embryonal tumors in instances where DNA methylation studies are not available.

12. Meconium Staining of the Amniotic Fluid and the Presence and Severity of Acute Placental Inflammation: A Study of Term Deliveries in a Predominantly African-American Population

*H Saeed[1], **S Jacques[2]**, F Qureshi[2];* [1]Henry Ford Hospital, Detroit, Michigan; [2]Wayne State University School of Medicine, Hutzel Women's Hospital, Detroit, Michigan

Background: There has long been controversy regarding the cause of meconium passage in utero; however, it is known that patients with meconium-stained amniotic fluid (MSAF) have a higher frequency of intraamniotic inflammation/infection than those with clear amniotic fluid (AF). It is also known that MSAF, particularly when thick, is associated with increased risk of perinatal complications and peripartum infection. Despite these associations, relatively few studies have specifically evaluated histologic acute placental inflammation in MSAF. In this study, we determine the frequency, stage, and grade of histologic acute maternal inflammatory response (MIR) and fetal inflammatory response (FIR) in term placentas with MSAF and compare these findings with those from a group with clear AF. We further compare these findings in thick compared to thin MSAF subgroups, this being the first study to do so.

Methods: Singleton term placentas with MSAF documented by visual observation at time of delivery (MSAF group, n=310) were evaluated for presence of histologic MIR and FIR, including stage and grade. These were compared with term placentas submitted by the obstetrician for pathologic examination for reasons of obstetric/neonatal concern other than MSAF and with clear AF (clear AF group, n=250). All were delivered during an 8-month period in 2014 and represent consecutively submitted placentas with appropriate criteria for inclusion. Clinical information was obtained from the maternal medical record. Stillbirth and major congenital malformations were criteria for exclusion.

Results: Histologic MIR was present in 57.7% of the MSAF group compared to 44.0% of the clear AF group (p=.001), while FIR was present in 40.3% of the MSAF group compared to 29.2% of the clear AF group (p=.008). Either MIR and/or FIR were present in 62.3 % of the MSAF group, compared to 48.0% the clear AF group (p=.001), while both MIR and FIR together were present in 35.8% of the MSAF group compared to 25.2% of the clear AF group (p=.008). Thick MSAF was associated with higher stage FIR compared to the thin MSAF subgroup (29.2% vs 5.4%, p=0.004); however, there was no significant difference in MIR stage, MIR/FIR frequency, or MIR/FIR grade between thick compared to thin MSAF subgroups. There was no significant difference in maternal medical conditions, cord arterial pH <7.0, or 5 minute Apgar score <7 between groups. The

mothers were predominantly African-American (80%).

Conclusion: Histologic MIR and FIR are frequent findings in term placentas with MSAF. Term placentas with MSAF more frequently exhibit MIR and FIR than placentas examined for clinical reasons other than MSAF. Thick MSAF is associated with higher FIR stage when compared to thin MSAF; however, this association is not seen with MIR.

13. Chemotherapy Use During Pregnancy: Proposing the Term Chemical Villitis. A Study of Nine Cases.

***D Kantarovich**, D Moncaleano, **N Khoshnam**, **B Shehata**;* Emory University School of Medicine, Atlanta, Georgia

Background: Cancer treatment during pregnancy can lead to various maternal complications including increased risk of infection, spontaneous abortions, maternal immunosuppression, anemia, and neutropenia. Although the use of chemotherapy during pregnancy can lead to detrimental effects for both the mother and the fetus, there has been limited focus on the effects of chemotherapy to the placenta.

Methods: After obtaining IRB approval, the files from our institution were reviewed to identify any cases of maternal use of chemotherapy during pregnancy. For the identified cases, the maternal history, infant information and placental examination were reviewed. The placental sections were examined using H&E stains. The available bacterial and viral cultures were reviewed. Additionally, we performed a panel of immunohistochemistry and PCR to identify any viral etiology.

Results: Nine cases were identified among 4,352 pregnancies (0.2%). The newborns of these nine cases were male:female (7:2). All pregnancies were singleton. The maternal age of those cases ranged from 23-35 (mean 32). The malignancy diagnosis included: cervical cancer (n=3), Leukemia (n=3), Breast cancer (n=2), and Hodgkin lymphoma (n=1). All patients were diagnosed and started chemotherapy in their second trimester. Five infants showed intrauterine growth restriction (IUGR), the placentas of those 5 cases were also small for gestational age. Histopathology revealed 3 placentas showing villitis of unknown etiology (VUE) and 1 showing chronic intervillositis (44%), which compared to VUE in the general population of 5-15%. Results of the viral and bacterial cultures and immunohistochemistry stains were negative. There was no evidence of hyperpolyploidization of the extravillous trophoblast.

Conclusion: In our three cases of VUE and one case of chronic intervillositis, the patients had been diagnosed with cancer and underwent chemotherapy during their second trimester of pregnancy. We are proposing the term medication induced villitis to describe our findings. This type of villitis is possibly due to detrimental effects of chemotherapy leading to the dysregulation of maternal T lymphocytes. Additionally, an unknown immune system suppression mechanism in those patients can be a contributing factor. Further studies are needed to fully understand the underlying mechanism.

14. Placental Microbiome, Cord Blood Microbiome, and Meconium Microbiome Are All Distinct at Term

***O Faye-Petersen**, A Yee, N Ambalavanan, C Lal;* University of Alabama at Birmingham, Birmingham, Alabama

Background: Recent studies indicate the existence of a placental microbiome (PMB) and challenge the dominant belief that the fetus develops in a sterile environment. Work by Aagaard, et al (Sci Transl Med.2014;6:237ra65), using whole genome sequencing metagenomic analysis of randomly selected snap frozen placental tissue samples from a repository of term uncomplicated deliveries, revealed healthy term placentas had a unique, low abundance community of endogenous bacteria with limited diversity that most closely resembled the nonpregant oral microbiome (MB). Bacterial operational taxonomic units (OTUs) in decreasing predominance of

detection in their study were: γ Proteobacteria (e.g., *Escherichia coli*), Bacteroides, Actinobacter, Firmicutes, Fusobacterium and Tenericutes. They proposed that oral microbiota were predominantly hematogenously translocated to the placenta and that the PMB plays important roles in gestation. Other investigations have identified different MBs in normal amniotic fluid and membranes, meconium, and cord blood (CB). However, the work by AAgaard et al and some other groups has been contested and is not yet replicated. Our objectives were to determine if: (1) we could confirm the existence of a PMB; (2) the amnion, parenchyma, and basal plate have similar MBs; and (3) CB and meconium have distinct MBs.

Methods: Case amniotic, parenchymal, and basal plate samples were taken from 24 term placentas immediately after delivery, in the operating room; this protocol markedly reduced risks of sample contamination. Case correlated CB and infant first meconium samples were also taken. All samples were snap frozen, processed for microbiome analysis by isolation of microbial DNA, creation of 16S V4 amplicon library, and DNA sequencing. Sequences were grouped into OTUs to Genera levels. Only samples with >1000 reads were included. Shannon diversity index (SDI) was calculated between groups.

Results: Phyla are listed in order of abundance (p-value <0.05) for each specimen and p-values for SDI follow. Placenta: Proteobacteria [Subphylum γ (Genus *Escherichia*)>> Subphylum β), Firmicutes, Bacteroides, Fusobacteria, and Tenericutes; among the 3 placental sample types, p-values for SDI= 0.3371 - 0.6464. CB: Firmicutes, Proteobacteria (Subphylum β>> Subphylum α), Bacteroides, and Fusobacteria. Meconium: Proteobacteria (Subphylum γ)>> Fusobacteria>> Bacteroides. Placental sample types:CB p-values of SDI= 2.164 e08 - 0.000174. Basal plate:Meconium SDI= 5.474e-08.

Conclusion: Our preliminary findings support the existence of a unique PMB, but we detected higher Firmicutes and lower Actinobacteria abundances than Aagaard et al. These variances may reflect a higher number of African-American patients in our cohort, our smaller study size, and/or our method of sample collection. Our placental data further indicate that 1) the amnion, parenchyma, and basal plate have an overall similar qualitative MB; 2) CB has a rich MB different from the PMB; and 3) postnatal meconium has a MB, but with significantly less abundance than the PMB or CB. A general limitation of PMB research is that detection of microbial DNA may not reflect the presence of *living* bacteria; studies addressing this uncertainty are ongoing and will help characterize the PMB.

15. Redness Discordance in Monochorionic Twin Placentas: Correlation with Clinical and Placental Findings

***M De Paepe**, F Gundogan, Q Mao, S Chu, S Shapiro;* Women & Infants Hospital, Providence, Rhode Island

Background: Recent studies suggest redness (color) discordance of the placental basal plate may be a marker for twin anemia-polycythemia sequence (TAPS), a monochorionic twinning complication characterized by marked intertwin hemoglobin (Hb) discordance in the absence of oligohydramnios-polyhydramnios. We determined the clinicoplacental and choriovascular correlates of basal plate color discordance in monochorionic twin placentas, and assessed its value as postnatal indicator of TAPS.

Methods: We performed a retrospective clinicoplacental analysis of 100 consecutive non-TTTS diamniotic-monochorionic twin placentas (>23 weeks gestation) with photographic documentation of the basal plate. Basal plate redness was quantified by computer-assisted analysis of digital images and expressed as intertwin color difference ratio (CDR).

Results: Intertwin CDR ranged between 1.01 and 2.79 (median CDR: 1.10). The 90th percentile CDR value (1.57) correlated well with the proposed CDR cut-off value for TAPS (1.5). The gestational ages, birth weights, cesarean

delivery rates and Apgar scores were similar in high (CDR > 1.5) and low CDR pregnancies. Twins with high CDR had significantly larger hemoglobin discordance than twins with low CDR (9.50 g/dL versus 2.15 g/dL, $P < 0.0001$). Color discordance was associated with striking paucity and/or small size of intertwin AA anastomoses (fraction with AA anastomosis: 31% versus 94%, $P < 0.001$) and decreased number of artery-to-vein anastomoses (median: 3 versus 9, $P < 0.01$). In 9/13 (69%) cases with high CDR, the putative flow direction, based on net number of AV anastomoses visible on the chorionic surface, was directed from pale placental share (donor) to polycythemic placental share (recipient). However, in 4/13 (31%) cases, the putative flow imbalance was directed from plethoric to anemic placental share. In two of these 'flow- and color-discordant' cases, deep artery-to-vein intertwin anastomoses in the expected pale-to-plethoric direction were readily identified, located below the amniochorion. Of the 100 monochorionic twin sets, nine (9%) qualified as *bona fide* TAPS, as currently defined. Of these 9 TAPS cases, 8 (89%) had a CDR >1.5. Conversely, 86/91 (95%) cases without TAPS had a CDR <1.5.

Conclusion: Significant color discordance (CDR > 1.5) was identified in 13% of non-TTTS monochorionic twin placentas, and correlated with Hb discordance and paucity of intertwin anastomoses. Our findings suggest CDR > 1.5 is a sensitive (89%) and specific (95%) postnatal marker of TAPS. The existence of sub-amniochorionic AV anastomoses may explain unanticipated outcomes in monochorionic twin pregnancies and may have implications for management of TAPS. The long-term neurodevelopmental consequences of severe intertwin Hb discordance and TAPS remain to be determined.

16. Recurrent Placental Massive Perivillous Fibrinoid Deposition and Previously Undescribed Co-occurrence of Multiple Large Nearly Confluent Subchorionic Thrombohematomas

V Duncan[1]*, A Sutton*[2]*, O Faye-Petersen*[3]*;*
[1]Seattle Children's Hospital Department of Pathology, Seattle, Washington; [2]University of Alabama at Birmingham Department of Obstetrics and Gynecology, Birmingham, Alabama; [3]University of Alabama Department of Pathology, Birmingham, Alabama

Background: Maternal floor infarction (MFI) and massive perivillous fibrinoid deposition (MPVFD) are rare, closely related entities of unclear etiology characterized by chorionic villous encasement by fibrinoid in patterns of basal rind-like (MFI) or varying degrees of lattice-like (MPVFD) parenchymal involvement. The spectrum is associated with fetal intrauterine growth restriction (IUGR), pregnancy loss, and high recurrence risks that may be improved by maternal gestational treatment with low molecular weight heparin (LMWH) and Aspirin (ASA). We report a case of recurrent MPVFD with previously undescribed co-occurrence of multiple massive subchorial thrombohematomas in a patient treated with LMWH and ASA.

Methods: A 24-year old G5P1131 woman treated with LMW/ASA prophylaxis since 7 weeks of gestation (wkG) for history of prior MFI/MPVFD diagnoses and pregnancy loss, had a midtrimester elevated maternal serum alpha fetoprotein (MSAFP) level of 8.56 multiples of the mean (MoM) and detection of fetal IUGR by ultrasound at 18.1 wkG. Onset of preeclampsia at 30.5 wkG prompted induction of labor and vaginal delivery of a small for gestational age female infant (weight/length <10%tile; head circumference 25%tile). Apgar scores were 1 and 7. The baby was admitted to the neonatal intensive care unit, but did well and was discharged at 6 wk of life. Past obstetric history included uncomplicated delivery of a term live-born infant (6 years prior to index pregnancy); fetal loss at 24.4 wkG (2 years prior) with history of midtrimester elevated MSAFP 22.8

MoM and ultrasonographic findings of severe oligohydramnios, IUGR, and placentomegaly; and missed abortions at 12.6 wkG (1 year prior) and 9 wkG (7 months prior.) Testing for antiphospholipid syndrome was negative. Paternity of the term infant was different from the other pregnancies.

Results: Examinations of the 24 wkG, 12 wkG, and 9 wkG losses revealed features of MPVFD. The 24 wkG placenta also showed acute chorioamnionitis and a 7x5 cm chronic subchorial thrombohematoma. The index placenta was 604g (249-584g expected.) Its umbilical cord was trivascular, hypercoiled (6 coils/10 cm), and had eccentric insertion. Bulging, 5.0 cm recent to chronic subchorial thrombohematomas affected 70% of the fetal surface. The maternal surface was pale and firm. Serial parenchymal sections revealed 2.0-4.0 cm thick, dense, granular, pale tissue with some small blood lakes and basal thrombohematomas. Microscopically, MPVD with extravillous trophoblastic proliferation extended into 50-80% of the transmural tissue thickness. Some thrombohematomas and infarctions were seen.

Conclusion: This is the first report of multiple large subchorial thrombohematomas developing in a setting of MFI/MPVFD. High grade MPVFD alters maternal space blood flow patterns and can result in infarctions, and in our case appears to have led to relative subchorial stasis and blood accumulations. Notably, the placenta from the 24wkG loss also had a large thrombohematoma that occurred in the absence of anticoagulant therapy. Finally, our report of recurrent MFI/ MPVFD in 4 sequential pregnancies with 3 losses with the same paternity and improved outcome with HMWH/ASA therapy supports the theory that alloimmune mechanisms play a part in at least some cases of MPVFD/MFI.

17. Pathologic Features of Placental Mesenchymal Dysplasia in Early Gestation

E Chan, J Wright JR, ***M Brundler****;* University of Calgary, Calgary, Canada

Background: Placental mesenchymal dysplasia (PMD) is a rare placental anomaly that can resemble partial hydatidiform mole (PHM) sonographically and pathologically. The pathogenesis of PMD is unclear, but androgenetic/biparental mosaicism has been the most consistent molecular aberration observed to date. PMD can coexist with a normal fetus, though Beckwith-Wiedemann (BWS)-like features are often seen. Differentiating PMD from PHM is crucial due to the vast difference in management. While the pathologic features of PMD in late gestation are well characterized, those in early pregnancy are poorly defined. We hereby report 3 cases of PMD diagnosed in the 1st and early 2nd trimesters. This is the first case series with detailed pathologic descriptions of PMD in early pregnancy.

Methods: Case series with review of placental pathology.

Results: Case 1 is a termination of pregnancy (TOP) at 12+5 weeks due to ultrasound findings of omphalocele and a cystic placenta suspicious for PHM. Case 2 is a TOP at 14+1 weeks due to ultrasound findings of a cystic placenta suspicious for PHM. Case 3 is a miscarriage at 17+5 weeks; ultrasound revealed omphalocele and a cystic placenta. Grossly, the placentas in the Cases 1&2 were fragmented and consisted of normal appearing villi admixed with grapelike vesicles. The placenta in Case 3 was intact, large, and featured numerous fluid-filled cysts on the fetal surface. Microscopically, in Case 1, a mixture of normal-appearing 1st trimester villi and hydropic villi with prominent cisterns, minimal trophoblastic proliferation and inclusions was noted. Microscopic features of Case 2 were similar to Case 1, but an increased number of peripherally located, small, thin-walled vessels with red blood cell extravasation was seen in some of the hydropic villi. Some vessels also started to assume a thick muscular wall. In Case 3, some of the enlarged villi

displayed a fibrous stroma. The muscular walls of the vessels were also more conspicuous and hyalinised. In all 3 cases, p57 stained cytotrophoblasts and scattered stromal cells in the normal villi, but only cytotrophoblasts in the hydropic villi, suggesting androgenetic/biparental mosaicism. Cytogenetic analysis demonstrated 46, XX in Cases 1&2. Findings in all 3 cases were compatible with PMD.

Conclusion: PMD should be included in the differential diagnosis of a placenta with cystic changes, particularly when a normal fetus or a fetus with BWS-like features is present. Our observations indicate that the classic histologic features of PMD, i.e. vascular ectasia and cirsoid vessels, are not well developed in early pregnancy. Absence of trophoblastic proliferation and inclusion also does not reliably distinguish PMD from PHM in early gestation. Aberrant p57 expression and a diploid karyotype help to differentiate PMD from PHM.

18. Incidence and Risk Factors for Chorioamnionitis in the US National Birth Registry

A Gilani[1]*, Z Siddiq*[2]*;* [1]Icahn School of Medicine at Mount Sinai, New York, New York; [2]Department of Obstetrics & Gynecology Columbia University Medical Center, New York, New York

Background: Chorioamnionitis (CA)- inflammation and/ or infection of the placental membranes is associated with adverse pregnancy outcomes including spontaneous preterm delivery, sepsis and neurological damage. The risk factors of CA are poorly understood.

Methods: We studied the prevalence of CA in the US Natality Database which represents data from over 99% of all live births in the US. Maternal and child characteristics from over 25 million live births spanning the study period (2005- 2013) were obtained from the National Center for Health Statistics and analyzed using the Statistical Analysis Software (SAS) v9.4 (Cary, NC).

Results: A total of 303,335 cases of CA were recorded in the database during the study period, translating to an overall incidence of 12.1 per 1,000 live births. Univariate analysis showed strong association with a short gestational age/ preterm delivery and low birth weight. No significant relationship was seen with maternal diabetes or hypertension or with socioeconomic indicators such as maternal educational achievement or self identified race. Further detailed analysis will look into any possible relationship of CA with neurological dysfunction, sepsis or neonatal distress.

Conclusion: Chorioamnionitis remains a major cause of morbidity in the US population with little change in incidence over the past decade. Although not designed to assess causality, this study confirms the strong association of CA with premature delivery and the associated low birth weight.

19. Occult Massive Visceral Fat Necrosis Following Therapeutic Hypothermia for Neonatal Encephalopathy.

S Khedr , *M De Paepe****,*** *A Piskorski, J Goldstein, A Laptook; Women* & Infants Hospital, Providence, Rhode Island

Background: Neonatal encephalopathy is associated with a poor outcome including cerebral palsy and neurodevelopmental/neurosensory impairment. Therapeutic hypothermia (whole-body cooling) improves survival and neurodevelopmental outcome in term newborns with moderate-to-severe encephalopathy. Complications of therapeutic hypothermia include hypoglycemia, hypotension, and thrombocytopenia. Rare cases of visceral fat necrosis have been described, uniformly accompanied by subcutaneous fat necrosis.

Methods: We report a case of clinically unsuspected, massive visceral fat necrosis in a resuscitated term infant with APGAR score 0 at 1 minute ("resuscitated apparently stillborn"), managed by therapeutic hypothermia.

Results: A 3580 g male infant was delivered at 38 weeks gestation to a 25-year-old

mother with history of insulin-controlled type 1 diabetes mellitus and hypothyroidism. Tight umbilical cord entanglement was noted at birth. APGAR scores were 0 at 1, 5, and 10 minutes, 2 at 15 minutes, and 4 at 20 minutes. The infant was severely encephalopathic and managed by whole-body cooling for the first 72 h of life. The NICU course was complicated by basal ganglia-thalamic neonatal encephalopathy, pulmonary hypertension, and ventilator-dependence. The infant expired on the 25th day of life. Postmortem findings included organomegaly and pancreatic findings consistent with maternal history of diabetes, as well as severe hypoxic-ischemic encephalopathy with multifocal cerebral and cerebellar infarcts. Strikingly, there was extensive necrosis of the visceral brown fat, involving thoracic, abdominal and retroperitoneal adipose tissue. This massive visceral fat necrosis was characterized by a granulomatous infiltrate of multinucleated giant cells, lipophages, and lymphocytes, associated with calcification. In contrast, there was a distinctive sparing of the subcutaneous (white) fat, which displayed only focal lipid crystalllization (a common postmortem finding).

Conclusion: This case of massive visceral (brown) fat necrosis in a term encephalopathic infant treated by whole-body cooling is exceptional in view of both the diffuse and the selective involvement of brown fat. The apparent differential sensitivity of brown and white fat to hypoxia and/or hypothermia may be attributable to their disparate biochemical characteristics. The fulminant - yet clinically occult - visceral fat necrosis seen in this case suggests that lesser degrees of fat necrosis may occur in distressed newborns without being recognized. The exact mechanisms underlying the observed fat necrosis remain undetermined. However, this case reinforces the importance of close monitoring of encephalopathic newborns for potential short-term (e.g. hypercalcemia) and long-term (e.g. scarring, sclerosis) sequelae of fat necrosis.

20. Gross Only Examination of Elective Termination of Pregnancy Specimens: an Evaluation and Recommendations

***H Pinar**, S Shapiro, L Young;* Women and Infants Hospital of Rhode Island, Providence, Rhode Island

Background: When the pregnancy is intentionally terminated prior to 20 weeks as a matter of the woman's choice it is called elective termination. In the United States, in 2008, there were 6.4 million pregnancies along 62 million women. 50% of pregnancies were unintended and 19% of the pregnancies resulted in pregnancy termination. Pregnancy termination is an integral part of obstetrics and gynecological care. According to CDC, the rate of pregnancy termination in the United States in 2008 was 16 per 1,000 women aged 15 to 44 years or 230 per 1,000 births. After the legalization of elective terminations, Healthcare Providers and insurance covered the procedure to various degrees. But over the years when the debate over terminations intensified individual states started to make certain decisions to compromise or limit the access of elected terminations to the young women who are the main recipients and customers of this procedure. With the expected decrease in health care funding especially for women's care, it is expected most of these services either to stop or may continue with possible requests from the pathologists to make some compromises to decrease the cost of the process.

Methods: In our Division, we prospectively analyzed 35 specimens received for diagnosis of products of conception requesting specifically "gross only" examination. The specimens were initially examined only visually and if no chorionic villi were seen, they were re-examined under a dissection microscope. When the perinatal pathologist's assistants could not reach a decision the responsible attending examined the specimen. When the attending pathologist also could not make a definitive decision, then all the pathologists (3) examined and rendered their opinions. These cases were then

submitted for processing and histopathological examination were performed.

Results: Our accuracy for determining the presence of chorionic villi was 45% for specimens from pregnancies of gestational ages less than 5 weeks. In all the other specimens older than 5 weeks and especially in the presence of embryonic or fetal parts, the accuracy reached 100%.

Conclusion: In the coming years, where health care of young and poor women is expected to almost totally disappears, the perinatal pathologists should be vigilant not to yield to pressure coming from the clinical care givers to compromise routine procedures for "savings" in health care allocations. We recommend any specimens from a pregnancy younger than 6 weeks gestational age to determine the presence of chorionic villi, the threshold for submitting tissue for processing and histological examination should be very low.

21. Development of an automated web based tool for reporting pediatric autopsies.

K Patel; Texas Children's Hospital, Houston, Texas

Background: Performance, work-up, and reporting of pediatric autopsies are complex activities requiring coordination and integration of several technical and non-technical steps. Standard pathology laboratory informatics systems (LIS) are not necessarily designed for this and often prove inadequate leading loss of time/efforts, potential for errors, higher turn-around time, poor customer satisfaction and eventually decreased autopsy rate. We aim to develop a web based tool and a potential knowledge-base to document and report perinatal and pediatric autopsies.

Methods: A web-based autopsy reporting system is developed on Ruby on Rails platform and the client side is built using Bootstrap and JavaScript. Use of the object relation mapping makes the back-end compatible with a variety of SQL/NO-SQL databases. The application is lean making deployment on local servers within institutional firewalls or on HIPAA protected cloud servers very easy. It can be used stand alone or in combination with existing pathology LIS such that the final report can be imported to be a part of patient's EMR.

Results: A website is created with role based login for secretaries, pathology trainees, pathologists and referring nurses/physicians with appropriate access/privileges for their part. Autopsies are divided into perinatal (those with placenta and/or mother's information) and pediatric type. Major sections include patient and mother's information, placenta, external and internal examinations, provisional and final diagnoses, ancillary tests, clinical summary, clinico-pathologic correlation and autopsy QA. Each section has several items with an ability to choose response/s from standard options as well as custom explanations. Age/gender related standards for internal and external examination are auto-extracted from published sources. Final report is partially auto generated and editable with an ability to import in various document editors such as Microsoft Word.

Conclusion: This system has several advantages over the existing manual way of documenting and reporting pediatric autopsies. Advantages for pathologists include: quick and precise availability of published standards for several parameters; a well-organized template for reporting that can be easily customized; paperless operation and an ease of search within the database for education/research purpose. Administrative advantages include: easy login management, minimal oversight, role based access management of various resources, integrated quality assurance, easy user interface, and semi-automated report generation that is compatible with several document editors including existing reporting systems.

22. Early unexplained deaths of Norwich Terrier puppies are associated with abnormal lung development and pulmonary vascular disease

K Williams[1]*, L Huang*[1]*, S Abman*[2]*, C Galambos*[2]*;*
[1]Michigan State University, East Lansing, Michigan; [2]University of Colorado, Aurora, Colorado

Background: Childhood interstitial lung diseases include several rare disorders that are characterized by developmental abnormalities of alveolar and vascular growth and are commonly fatal. Insights into basic mechanisms that contribute to developmental lung disorders are necessary to understand underlying pathomechanisms, improve the identification of at risk newborns and to design future interventions. However, spontaneous mammalian animal models to study human neonatal lung disease are lacking. Recently, we have identified abnormal lung development in several breeds of domestic dogs, which may be an under-recognized cause of neonatal mortality in puppies. Sudden unexplained death in Norwich Terrier (NT) puppies has been recognized, however, the underlying cause is unknown. Based on these findings, we hypothesized that abnormalities of lung development contribute to high mortality of NT puppies; further this may provide a unique model to study mechanisms of developmental lung disease in humans.

Methods: Lung tissue from NT puppies with spontaneous demise < 1 month of age were collected. Complete autopsies were performed and the lungs were inflation-fixed with 10% neutral buffered formalin. Sections of right and left cranial and caudal lung lobes were routinely processed and HE stained sections were evaluated. One age matched control with no known respiratory pathology was also included.

Results: Five female and four male puppies were identified with the average age of 10.5 days (range: 1 day – 25 days). Reported clinical signs consisted of poor weight gain, failure to thrive and tachypnea. Lungs were mottled, but otherwise lacked gross structural abnormalities. There were no congenital cardiac anomalies and the main pulmonary vessels appeared grossly normal. All lung sections of each of the NT puppies showed marked histologic signs of abnormal distal lung structure. The acinus appeared underdeveloped with decreased septation of distal airspaces and marked thickening and hypercellularity of alveolar septa. Small pulmonary arteries were markedly remodeled, with smooth muscle thickening. Double capillary layers as well as dysplastic capillaries within the interstitium were often present. Aberrant bronchopulmonary anastomotic vessels were occasionally noted.

Conclusion: We report that early deaths in NT puppies are associated with striking signs of developmental lung vascular and airspace disease, including evidence of decreased alveolarization, interstitial thickening, pulmonary vascular remodeling, and prominent capillary growth. We speculate that genetic and molecular studies of lung development in NT puppies may provide novel insights into human developmental lung disease.

23. Histologic Features of Impaired Lung Development Identify a Subset of Infants with Sudden Unexplained Infant Death (SUID)

C Galambos*, D Bush*[1]*, S Abman*[1]*, M Caplan*[2]*;*
[1]University of Colorado School of Medicine/Children's Hospital Colorado, Aurora, Colorado; [2]Suffolk County Office of the Medical Examiner, Hauppauge, New York

Background: Despite advances regarding risk factors associated with sudden unexplained infant deaths (SUID), about 3,500 US infants still die suddenly and unexpectedly each year in the US and SUID remains a major public health concern. SUID has been linked to severe hypoxemia, yet mechanisms that contribute to hypoxemia in SUID are poorly understood. Early studies reported abnormalities of the pulmonary circulation, including increased pulmonary artery (PA) smooth muscle thickening, suggesting an association of SUID with chronic hypoxemia. It remains unknown, however, how changes in the PA contribute to

the pathophysiology of SUID. Two past studies of infants and children suggested intrapulmonary arterio-venous shunt as a pathomechanism for sudden death, however, identification of the anatomical basis for this hypothesis was lacking. Recently, we have characterized prominent anastomotic connections between the pulmonary and bronchial circulations (intrapulmonary bronchopulmonary anastomoses, IBA) in several neonatal lung disorders that likely contributed to right to left shunting associated with early death. However, whether IBA represent the anatomic basis of the previously demonstrated intrapulmonary arteriovenous anastomoses in SUID is unknown. We propose that underdeveloped pulmonary vasculature and the presence of IBA characterize a subset of patients with SUID.

Methods: We collected 10 SUID cases with comprehensive clinical data including potential for mechanical asphyxia, post-incident survival interval, and relevant autopsy findings including cause of death, manner of death, and significant risk factor(s) for death, along with histology data including the presence of IBA, PA thickening, hemangiomatosis pattern, and alveolar growth abnormality. We performed 3D reconstruction in one SUID case. We also collected 1 age matched control case (death was due to drowning).

Results: Nine of the 10 SUID cases had potential mechanical asphyxia. Eight cases had IBA, 6 had PA thickening, 6 had hemangiomatosis pattern, and 4 had decreased alveolar growth. The control case did not show any of these findings. Of the SUID infants, lung histology showed that 6 had IBA (60%), 5 had PA thickening (50%; all had IBA), 5 had hemangiomatosis pattern (50%; all had IBA), and 3 had impaired alveolar growth (30%; 1 had IBA).

Conclusion: We report a high rate of abnormalities of lung development in young infants dying with SUID that include the presence of IBA, hemangiomatoisis and abnormal lung vascular and alveolar structure. These findings strongly support our hypothesis that a subset of SUID patients have striking abnormalities of lung growth, and we speculate that abnormal lung structure including IBA with pulmonary vascular disease increases the risk for SUID.

24. Alteration of airway smooth muscle in congenital pulmonary airway malformation

Y Jiang, F Yang, Y Luo, S Zhou, W Shi, ***L Wang****;* Children Hospital Los Angeles, University of Southern California, Los Angeles, California

Background: Congenital pulmonary airway malformation (CPAM) is characterized by multiple lung cysts in young children. It is postulated that most CPAM develops during the prenatal lung development when there is rapid expansion of the conducting airway and peripheral lung tubule. In our previous study on lung development of fetal mouse, we found that defective airway smooth muscle cell growth alters airway branching and budding, causing airway cystic lesions in fetus. However, the pathogenic process and mechanisms in human CPAM remain unknown.

Methods: To investigate whether defective airway smooth muscle cell development is associated with airway cyst formation in patients with CPAM, we retrospectively examined 20 lung specimens from patients with CPAM II (1-2 years of ages) and 7 age-match lung tissue as controls from a single institute. Immunohistochemical and immunofluorescent studies including ACTA2, TUBB4A, and SCGB1A1 were performed. Length of smooth muscle layer around airway circumference, average thickness and total area of airway smooth muscle layer were quantified using Image J imaging software. Student's t-tests were used for statistical analysis.

Results: We found that 1) layer of smooth muscle underlining the airway cysts in patients CPAM II was thinner and smaller than those around normal bronchioles in controls. 2) Club cells were found in both normal and cystic epithelia, but number of Club cells in cysts of CPAM II was significantly decreased. 3) tufts of mucogenic cells were present in cysts of 28% patients with CAPM II. 4) airway smooth muscle

area, length, and thickness in the cysts in CAPM II were significantly reduced compared to those in controls ((p<0.05).

Conclusion: Our results indicate that defect in airway smooth muscle cell development may play a role in CPAM II pathogenesis, and that decrease in Club cells may be associated with CPAM II development.

25. Expanding The Spectrum of Childhood Pneumoconiosis: The Role of Histopathology, Electron Microscopy, and Energy Dispersive X-Ray Spectroscopy

B Siegele[1]*, E Wartchow*[2]*, R Deterding*[3]*, J Weinman*[3]*, C Galambos*[3]*;* [1]Boston Children's Hospital, Boston, Massachusetts; [2]Children's Hospital Colorado, Aurora, Colorado; [3]Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado

Background: Pneumoconiosis (PC) is caused by chronic dust exposure and is considered an occupational lung disease. In the west children are generally protected from such exposures, and cases of childhood PC are exceedingly rare. In the current era of a growing number of child refugees in the US, some with smoke exposure histories, combined with increased access to cannabis products among teenagers, a novel spectrum of childhood PC could be considered. PC is known to increase the risk of lung infection and can cause complex lung disease, making recognition of this entity in lung biopsies crucial in guiding management. We aim to characterize lung histology, ultrastructure, and energy dispersive x-ray spectroscopy (EDS) findings and to correlate these with clinical and imaging results for two children exposed to biomass smoke ("hut lung") and marijuana smoke.

Methods: We collected the following data: age, sex, exposure history, clinical presentation, computed tomography (CT) findings, and lung biopsy findings from light microscopy, electron microscopy (EM), and EDS.

Results: Case 1. 15 year-old female Nepali refugee with biomass smoke exposure presented with productive cough and hemoptysis, and was treated for suspected active tuberculosis. CT showed cystic and varicoid bronchiectasis and centrilobular micronodules in bilateral lower lobes. A lung biopsy identified black pigment with birefringent needle-like material, chronic bronchitis, emphysema, bronchiectasis, and a mycetoma. EDS of birefringent material showed a predominance of aluminum silicate signal, with additional signal for potassium.

Case 2. 17 year-old male with daily marijuana inhalation presented with one month of progressive dyspnea and cough followed by acute hypoxic respiratory failure. CT identified centrilobular pulmonary nodules with associated ground glass opacities. A lung biopsy showed black pigmented deposits with birefringent crystals, a vaguely formed parenchymal granuloma with eosinophils, and eosinophilic pleuritis. EM highlighted crystalline inclusions within interstitial macrophages. EDS of crystalline inclusions is predominated by aluminum silicate signal, with additional signals for magnesium, potassium, iron, and titanium.

Conclusion: We expand the spectrum of childhood PC by correlating the clinicopathologic features of two children with non-occupational dust exposure. Pediatric pathologists should consider the diagnosis of PC in lung biopsies with appropriate clinical history, imaging data, and by recognizing the presence of scattered black pigment with polarizable needle-like crystals. EM coupled with EDS is key to the identification of xenobiotics and to ongoing efforts to correlate mineral type with prognosis. Treatment involves cessation of exposure and supportive care.

26. Pathologic spectrum of pediatric sellar and suprasellar lesions: an institutional experience

H Wang*, J Liang;* Vanderbilt University Medical Center, Nashville, Tennessee

Background: Primary lesions arising in the sella turcica and the suprasellar region in children may exhibit a wide range of clinical and radiographic presentations, depending on the primary location and size of the lesions. A broad spectrum of pathologic processes may be encountered, including common, benign lesions

and rare, malignant tumors with similar clinical and radiographic presentations. We aimed to assess the incidence of various sellar and suprasellar lesions diagnosed in our institution over the past 18 years, and characterize rare, malignant tumors that may be diagnostically challenging.

Methods: We performed a retrospective study (1999-2017) of all pediatric patients with biopsied or resected lesions in the sellar and suprasellar region. Non-diagnostic or indeterminate cases limited by tissue sampling were excluded.

Results: A total of 117 patients were identified (F:M 1.3; age 0.5-20, average 11.8 years). Of these, 110 (94.0%) were benign and 7 (6.0%) were malignant. All malignancies were primary tumors, including germinoma (n=5, 4.2%), primitive neuroectodermal tumor (n=1, 0.9%) and high grade neuroendocrine tumor (n=1, 0.9%). Among the benign lesions, the most common neoplasm was pituitary adenoma (n=36, 30.7%), followed by craniopharyngioma (n=28, 23.9%), pilocytic/pilomyxoid astrocytoma (n=24, 20.5%), Langerhan cell histiocytosis (n=2, 1.7%), mature teratoma (n=1, 0.9%), meningioma (n=1, 0.9%), schwannoma (n=1, 0.9%) and ganglioglioma (n=1, 0.9%). Other benign lesions included cystic (Rathke's cleft cyst, n=9; dermoid cyst, n=2; arachnoid cyst, n=1; ependymal cyst, n=1; encephalocele, n=1), inflammatory (lymphocytic hypophysitis, n=1), and hyperplastic (pituitary nodular hyperplasia, n=1). The clinical and radiographic presentations of primitive neuroectodermal tumor and high grade neuroendocrine tumor closely mimicked suprasellar craniopharyngioma and sellar pituitary macroadenoma, respectively. Most patients with germinoma presented with a sellar/suprasellar heterogeneously enhancing mass with hypopituitarism and/or visual disturbance, mimicking aggressive pituitary adenoma. While 33 of 36 children with pituitary adenoma were 13 years or older, 6 of 7 patients with malignant neoplasms were 12 years or younger.

Conclusion: Majority of pediatric sellar/suprasellar lesions are benign, with pituitary adenoma being the most common, followed by craniopharyngioma and pilocytic/pilomyxoid astrocytoma. The most common pediatric sellar/suprasellar malignancy is germinoma. Age appears to be useful for differentiating sellar/suprasellar malignancies from their close mimic pituitary adenoma.

27. The Role of Analytical Electron Microscopy in Pediatric Pathology Practice

***E Wartchow**, C Galambos;* Children's Hospital Colorado, Aurora, Colorado

Background: Analytical electron microscopy (AEM) is the combination of electron microscopic (EM) imaging and elemental analysis using energy dispersive x-ray spectroscopy (EDS). Interaction between the electron beam and a sample generates element-specific x-rays which are collected and used to identify the chemical composition of the area of interest. While commonly employed to aid in the specific characterization of asbestos-related diseases in adults, AEM can also provide identification of unknown xenobiotics within the pediatric population. In this study, we aim to demonstrate the versatility of AEM by presenting examples of cases in which AEM was used to identify the chemical composition of clinically significant particulates observed within solid tissue biopsies.

Methods: Examples of 3 cases in which AEM was utilized to provide important diagnostic information are presented. In each case, during routine investigation a foreign material was observed within the tissue biopsies prompting the decision to proceed with EM imaging and EDS study. The resulting chemical spectrum characterized the foreign material, which was then used to aid in identifying the source and assessing the pathologic risk of the exposure.

Results: The histologic, electron microscopic and elemental analysis of foreign material in each case is presented. Case 1: Dark particulate is observed within a fibrovascular

tissue mass adjacent to the site of orthopedic hardware removal. EDS reveals particles composed of titanium and vanadium, consistent with the hardware alloy. Case 2: Vacuolated macrophages in a muscle biopsy from a case of suspected metabolic storage disorder are shown to contain aluminum. The EDS data combined with additional clinical information suggested a diagnosis of macrophagic myofasciitis, a persistent inflammatory myopathy associated with aluminum-containing vaccine injections. Case 3: The observation of lung nodules prompted biopsy for concern of infection vs PTLD. Inhalation injury was suggested following the observation of interstitial macrophages containing black pigments containing birefringent crystalline material composed of aluminum silicate and other metals including magnesium, potassium and iron.

Conclusion: AEM is a technique underutilized by pediatric pathology practice and we propose it should be considered when unexplained foreign material within tissue biopsies is encountered. The analytical characterization of the unknown material complements the morphologic findings and together may provide important epidemiologic, diagnostic and management information.

28. INI1-Deficient Thymic Carcinoma in Young Children: A New Member of Rhabdoid Tumor Family

S Lummus1, *X Liang[1], K Capocelli[1], J Black[1], M Lovell[1], C Galambos[1], G Mierau[2], E Wartchow[2];*
[1]Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; [2]Children's Hospital Colorado, Aurora, Colorado

Background: INI1 is a core subunit protein in the SWI/SNF pathway encoded at 22q11.2. Loss of INI1 is found in malignant rhabdoid tumors usually occurring in the kidney, CNS, and soft tissue of young children. The cell of origin for such tumors is unclear due to their polyphenotypic pattern. ATRT also expresses neural marker GFAP in addition to epithelial & mesenchymal markers that other rhabdoid tumors carry. Although the family of INI1-deficient neoplasms is expanding, thymic carcinoma with rhabdoid features and loss of INI1 expression has never been described. We report 2 cases of INI1-deficient thymic carcinoma and characterize their clinicopathologic features.

Methods: Patients < 20 years old with thymic carcinoma were searched at our institution (2000-2016). A large study of pediatric thymic carcinoma from Europe (Eur J Cancer, 2015) was selected for comparison.

Results: Case 1: A biopsy of a large anterior mediastinal mass from a 21-month-old male showed sheets of large malignant epitheloid cells with abundant pale-pink cytoplasm and round-oval nuclei. Tumor cells were vimentin+, cytokeratin+, EMA+, CD5+, CD34+, CD3-, CD30-, CD117-, PLAP-, NUT-, S100-, and INI1-. EM showed intercellular junctions and short curving arrays of cytoplasmic filaments without desmosomes. Karyotype was 46,XY,t(6;22)(q13;q11.2). The diagnosis was thymic carcinoma with rhabdoid differentiation. The patient was treated with chemotherapy and died of disease at age of 23 months.
Case 2: A biopsy of a large anterior mediastinal mass from a 2-year-old female showed sheets of large malignant cells with the similar morphology to that seen in Case 1. Tumor cells were vimentin+, cytokeratin+, EMA+, S100+, CD5+, CD3-,
CD30-, CD34-, CD117-, PLAP-, NUT-, and INI1-. EM showed bundles of cytoplasmic filaments organized into paranuclear whorls, polyparticulate glycogen, no intercellular junctions. FISH was negative for chromosome 22 abnormalities. The patient was diagnosed as thymic carcinoma with rhabdoid differentiation and was treated with surgical resection, chemotherapy and BMT and is alive for 1.5 years.
European Study included 20 cases with a mean age of 13.1 years (4-19 y) and M:F=14:6. Treatment included chemotherapy and/or radiation. 75% (15/20) of patients died of disease. INI1 status is not recorded.

Conclusion: 1. Our cases suggest that thymic carcinoma in young children can show

rhabdoid features, loss of INI1, and reactivity for the thymocyte marker CD5 expanding the differential diagnosis of anterior mediastinal tumors.
2. INI1-deficient tumors have no specific cell origin or uniform morphology.
3. INI1 gene abnormalities appear to be the common step of tumorogenesis shared by tumors from a variety of anatomic location and morphology.
4. At least some of INI1-deficient tumors appear to carry the phenotypic imprint of their organ of origin (ATRT: GFAP; thymic CA: CD5), which may facilitate more accurate diagnosis.

29. Teratomas in Pediatric Patients: A Clinicopathologic Correlation Study

A Farooq1, *L Parsons[2], J Jarzembowski[2];* [1]Medical College of Wisconsin, Milwaukee, Wisconsin; [2]Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, Wisconsin

Background: Teratomas are a diverse group of neoplasms, heterogenous with respect to their composition of embryonic layers represented, their location, the presence of immature elements, and their coexistence with either somatic malignancy or malignant germ cell tumors. We sought to determine whether any significant correlations exist between various clinical and pathologic factors in pediatric teratomas that could provide useful insight into clinical behavior and prognosis.

Methods: We searched the surgical pathology database for teratomas diagnosed between the years of 1988 and 2016. Tumor site and size were acquired from the original surgical pathology reports, and all original slides from each case were reviewed for tissue types present, immature elements (including grade), and coexisting germ cell tumors/somatic malignancies. Clinical data obtained from the electronic medical record included age, sex, serum tumor marker levels at diagnosis, metastasis/recurrence, and date of death/last follow up. Component frequencies were compared by Student t-tests and correlation coefficients were calculated for relationships with potential clinical factors.

Results: Initially, 296 teratoma cases were identified; 188 were selected at random for review, comprised by the following sites: ovary 86 (46%), sacrococcygeal 33 (18%), testis 19 (10%), mediastinum 17 (9%), head & neck 15 (8%), abdominal/ retroperitoneal 11 (6%), and central nervous system 6 (3%). The most common elements were mature neuroglia (69%), respiratory-type epithelium (67%), and skin (52%). Lung tissue was more common in mediastinal tumors (12%) than other sites (1.2%), and pancreas was rarer in gonadal tumors (3.8%) than elsewhere (18%). The distribution of endoderm-, ectoderm-, and mesoderm-derived components did not differ significantly by anatomic site. Individual tumor components did not occur together with any particular predilection. There was no significant correlation between tumor composition and other clinical factors such as age, serum tumor marker levels, or survival.

Conclusion: Our study shows that the heterogeneity of tumor components in teratomas is not significantly restricted by anatomic site, and does not by itself determine prognosis or appear to correlate with other clinical factors. Additional studies are warranted to help understand the pathogenesis of these unique lesions and to better predict their clinical behavior and direct therapy.

30. Pediatric Breast Phyllodes Tumors: A study of 8 cases and review of the literature.

S Hafeez*, A Ricci, F Balarezo;* Department of Pathology and Laboratory Medicine, Hartford Hospital and Conn, Hartford, Connecticut

Background: Phyllodes tumors (PTs) are rare tumors that account for 0.3-1% of all breast primary tumors and 2.5% of all fibroepithelial tumors of the breast. Reported recurrence rates are 10-17% for benign tumors, 14-25% for borderline tumors and 23-30% for malignant PTs. They occur predominantly in middle-aged women. In 1998, Rajan et al reported a series of 45 cases of PTs in patients 24 years and younger, but cases reported in pediatric

patients are even more uncommon. We report a series of eight children/adolescents with breast masses which showed histopathologic features of benign phyllodes tumor.

Methods: Eight cases of PTs in pediatric patients were identified in our files from 2010 to 2017. Glass slides were available for all cases. Classification of the tumors was based on the WHO criteria for PTs.

Results: The age of the patients ranges from 14 to 17 years (mean 15.2 years). Tumor size ranges from 2.2 cm to 7.2 cm (mean 4.36 cm). Both breasts were affected equally. All patients were treated by local excision. Histologically, all tumors showed well-defined/pushing borders and <5 mitoses/10hpf. There was minimal stromal atypia and focal stromal overgrowth. 5/8 tumors showed mild stromal cellularity, and 3/8 showed moderate stromal cellularity. Using the WHO criteria, all tumors were diagnosed as benign PTs. 5/8 tumors abutted the surgical margin, and in 3/8 tumors (including the tumor with recurrence) the surgical margin was focally positive. Follow-up was available for all cases for a mean of 27.5 months. Local recurrence was reported in one case (12.5%). The cellularity and mitotic activity of the recurrent PT were similar to the original tumor (mild cellularity, 1 mitosis/10 hpf). At last follow-up all patients were alive with no evidence of disease.

Conclusion: Pediatric breast PTs show similar recurrence rates than tumors in adult patients. Reliable histologic predictors of local recurrence were not identified in this series. PTs in this age group should be treated to maximize breast conservation.

31. Maspin Expression in Pediatric Tumors

A Hopp[1], A Mackinnon[1], J Jarzembowski[2], ***L Parsons[2];*** [1]Medical College of Wisconsin, Milwaukee, Wisconsin; [2]Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, Wisconsin

Background: Molecular mechanisms in cancer are complex and include the interplay of numerous oncogenes and tumor suppressors. Maspin, a serine protease inhibitor, plays a role in metastasis suppression in adult epithelial malignancies, and its immunohistochemical (IHC) expression correlates with stage and survival in adult studies. To date, however, maspin expression has not been characterized in pediatric tumors.

Methods: Following IRB approval, tissue blocks containing tumor obtained at initial diagnosis were identified from 116 tumors: neuroblastic tumors of various subtypes (32), Wilms tumor (15), rhabdomyosarcoma (RMS; 16), Ewing sarcoma/peripheral neuroectodermal tumor (EWS/PNET; 10), rhabdoid tumor and atypical teratoid/rhabdoid tumor (5), hepatoblastoma (3), desmoplastic small round cell tumor (1), and a variety of non-Hodgkin lymphomas (34). Tissue microarrays (TMAs) were constructed with each tumor represented in at least triplicate; automated IHC for maspin was performed per manufacturer protocol. TMAs were scored for maspin staining intensity and extent (based on % tumor cells with nuclear staining) in a blinded fashion by two pathologists. Scores from all TMA cores for each case were averaged for both intensity and extent, and expression product was calculated as intensity x extent. Age at diagnosis and death/last follow-up, gender, and stage at diagnosis were obtained from the electronic medical record. Comparison of expression between tumors was performed using Student t-tests; correlation coefficients between expression and clinical factors were also calculated.

Results: Of the 116 study cases, 74 (63.8%) showed at least focal nuclear maspin expression. Among all tumors, maspin was expressed least frequently in Wilms tumor cases (40.0%, $p = 0.040$). Maspin mean expression product was greatest for EWS/PNET (2.25; $p= 0.047$) and for RMS (2.06; $p = 0.041$). When analyzed by RMS subtype, alveolar RMS expressed maspin in 100% of cases with a mean expression product of 3.56, which was significantly greater than both the overall mean expression product for all tumors (1.36; $p < 0.0001$) and the mean expression product for embryonal RMS (1.17; $p = 0.004$). Significant

correlation between maspin expression and clinical variables was not observed.
Conclusion: To our knowledge, ours is the first study to demonstrate expression of maspin in pediatric tumors. Maspin expression was significantly greater in alveolar RMS and EWS/PNET than other tumor types examined. Our findings warrant further investigation of maspin staining and correlation with clinical parameters in these specific disease cohorts; this, in turn, may help delineate maspin's potential role in the pathogenesis of these tumor types, as well as its value as a prognostic factor or therapeutic marker.

32. Rhabdomyosarcomas Associated with Ovarian Sertoli-Leydig Cell Tumors Express SALL4

***D Olson**, C Galambos, M Lovell;* University of Colorado Denver/Children's Hospital Colorado, Aurora, Colorado

Background: Ovarian Sertoli-Leydig cell tumors (SLCT) tumors are rare and intermediate- to poorly-differentiated SLCT have an adverse prognosis. SLCT with heterologous elements have a poor prognosis, particularly if associated with mesenchymal elements. We present three cases of intermediate- to poorly-differentiated SLCT with heterologous elements including a component of rhabdomyosarcoma (RMS) that unexpectedly demonstrated SALL4 immunoreactivity.
Methods: Histologic review with special studies and clinicopathologic correlation of three consult cases.
Results: Patients were between 14 to 16 years and the ovarian masses ranged from 18 to 22 cm. Presenting symptoms included abdominal fullness, vomiting and pain. Histologic sections revealed markedly heterogeneous neoplasms with variably differentiated Sertoli cell populations. Closely associated with the Sertoli cells were Leydig cells that diminished in number as the Sertoli cells became more poorly differentiated. Both populations were immunoreactive with inhibin and calretinin, although both were stronger in the Leydig cells. A third cell population with rhabdomyoblastic differentiation labeled with desmin and transitioned into a histologically undifferentiated spindle cell population intricately intertwined with the most poorly differentiated areas of Sertoli cells. This undifferentiated population had high mitotic activity and labeled with myogenin and MyoD1, diagnostic of RMS. SALL4 immunohistochemistry, performed to rule out a germ cell component, was unexpectedly positive in the RMS cells. Chemotherapy for all 3 patients was tailored to treat both RMS and SLCT. One patient was negative for germline DICER1 mutations; testing for the other two is pending. All 3 patients are alive 1 to 12 months post-diagnosis. Two have completed therapy without evidence of disease recurrence.
Conclusion: Intermediate- to poorly-differentiated SLCT with heterologous elements have a poor prognosis especially when a mesenchymal component is present. RMS rarely expresses SALL4, yet all 3 cases presented here showed reactivity in the rhabdomyosarcomatous elements. The significance of this finding in SLCT is unclear; however, SALL4 expression portends a worse prognosis in hepatocellular carcinoma and hepatoblastoma and has been suggested as a potential therapeutic target. Additional studies are needed to determine the significance of SALL4+ RMS in SLCT and whether it could serve as potential therapeutic target to improve outcomes.

33. Esophagitis Dissecans Superficialis; A Rare Diagnosis in Pediatrics with a Variety of Etiologies

***L Westbrook**[1], K Capocelli[2], A Treece[2];*
[1]University of Colorado at Denver, Anschutz Medical Campus, Aurora, Colorado; [2]Children's Hospital Colorado, Department of Pathology, Aurora, Colorado

Background: Esophagitis dissecans superficialis (EDS) also known as "sloughing esophagitis" is an uncommon disorder characterized by a variable extent of desquamation of the superficial esophageal epithelium. This entity has been reported in a

range of clinical settings including use of certain medications, consumption of hot beverages, celiac disease, chemical irritation, autoimmune bullous dermatoses, impaired motility, severe smoking, and idiopathic. The condition is felt to be benign with no known long-term complications. Typically seen in the elderly with a mean age of onset in the seventh decade, this is a very unusual diagnosis in pediatric pathology. We sought to review cases of EDS identified in our pediatric population.

Methods: A search of the pediatric hospital database for the previous 10 years (01/01/2007 – present) for the term "esophagitis dissecans superficialis" returned 2 cases in which EDS was the final diagnosis. Clinical presentation, past medical history and histologic features were compared between the two cases.

Results: Both patients were females in the adolescent to young adult age groups who presented with a chief complaint of dysphagia. Histologically, both cases showed similar features with characteristic "two-toned" squamous epithelium comprised of a superficial eosinophilic, necrotic layer and an underlying basophilic, viable layer separated by vacuolization or a smooth plane of dissection. Both lacked abundant inflammation. The greatest variation between the two patients was in their past medical histories. One patient had a history significant for myelodysplastic syndrome status post bone marrow transplant complicated by graft versus host disease (GVHD) and polypharmacy and was undergoing extracorporeal photopheresis therapy. In this patient, apoptotic keratinocytes were scattered throughout the epithelium suggesting that GVHD, in addition to possibly her polypharmacy, was contributing to the etiology of her EDS. The second patient had a history significant for spinal muscular atrophy type 2 who was taking multiple oral medications daily. Upon admission, it was found that she had some degree of esophageal dysmotility. Pill debris was identified within her esophagus during endoscopy as well as in histologic sections of biopsy material. In this patient, EDS was felt to be secondary to pill-induced contact injury and some degree of esophageal dysmotility.

Conclusion: Although uncommon, EDS does occur in the pediatric and young adult population, and given the array of clinical scenarios in which the entity presents, EDS should be considered in the differential for many esophageal disorders.

34. **Pediatric Eosinophilic Esophagitis is Associated with Increased Lamina Propria Immunoglobulin G4-Positive Plasma Cells**

J Bush[1]*, N Mohammad*[1]*, V Avinashi*[2]*, E Chan*[2]*, B Vallance*[2]*, E Portales-Casamar*[2]*,;* [1]University of British Columbia, Department of Pathology, Vancouver, Canada; [2]University of British Columbia, Department of Pediatrics, Vancouver, Canada

Background: Eosinophilic esophagitis (EoE) is widely considered to be a Th2-mediated food allergy condition that eventually leads to submucosal fibrosis and strictures. Recent studies, primarily focused on adults with EoE, demonstrated there is a strong association of EoE with IgG4 immunostaining and serum IgG4 levels. Few pediatric patients were studied however. Our study aimed to determine the role of IgG4 in pediatric EoE patients.

Methods: Using our local EoE clinical registry, we identified 41 EoE patients with sufficient submucosa to evaluate for plasma cells. We used 10 age and sex-matched controls with no diagnostic abnormalities in the esophagus at endoscopy or on biopsy. Using a monoclonal antibody to IgG4, we determined the maximum density of IgG4-positive plasma cells per high-power field (hpf). Using a qualitative assessment, we also graded the interstitial staining of the submucosa and epithelium.

Results: Our EoE cohort consisted of predominantly males with an average age of 5.9 years and 63% had a documented food allergy. Average peak eosinophilia was 49.3 eosinophils/hpf and the average IgG4-positive plasma cell density was 37.3/hpf in the active esophagitis patients, compared to 0.8 IgG4-

positive plasma cell/hpf in the negative controls. In patients with follow up endoscopy available, the density of IgG4-positive plasma cells was significantly higher in those with a food allergy than those that did not have a food allergy.

Conclusion: We demonstrate that active esophagitis in pediatric EoE patients is associated with IgG4-positive plasma cells, with this association being stronger for those with a documented food allergy. Previous studies have shown that EoE can be differentiated from reflux esophagitis by IgG4 staining, that EoE is associated with IgG4 in adults, and that food-specific serum IgG4 antibodies are seen within EoE patients. This current study, with these previous reports, further suggest that IgG4 may have a role in EoE pathophysiology.

35. Caroli syndrome; An Underrecognized Histologic Entity with Indications for Early Transplantation

A Greer[1]*, K Capocelli*[2]*, H Fenton*[1]*;* [1]Anschutz Medical Campus, University of Colorado at Denver, Aurora, Colorado; [2]Children's Hospital Colorado, Aurora, Colorado

Background: Caroli disease (CD) is both a sporadic and autosomal recessive congenital disorder of the liver with a prevalence of 1 case per 1 million people. It is manifested by segmental, multifocal cystic dilatation of intrahepatic bile ducts and, although present at birth, can clinically present at varying times in children and adults. Caroli syndrome (CS) is a more common variant with the bile duct dilation in associated with congenital hepatic fibrosis. Symptoms include recurrent biliary infections, portal hypertension, sequelae of cirrhosis, or even recurrent cholangiocarcinoma. Diagnosis can be challenging and a delay in treatment deadly. In patients with CS treatment is often liver transplantation and can be successfully performed even in very young children (J. Pediatr Surg 2011;46:638-641). We sought to review our experience with CD/CS, and evaluate histology findings and outcomes for patients with CS.

Methods: Database searches at our adult and pediatric hospitals, from 01/01/2000 - present, generated 7 cases using the textwords Caroli/Carolis, respectively, in which the diagnosis had been made, or considered. Of the 7 patients, 3 were diagnosed at a young age with CS. Clinical presentation and histological features were compared and contrasted between patients with CS.

Results: Of the 5 cases seen at our adult hospital, CD was considered in 4 patients, and CS documented in 1 autopsy case. The 17 year old whose autopsy was performed at our institution was diagnosed with CD at a young age with development of esophageal varices and portal hypertension. She primarily was treated for symptomatology, undergoing a segmental liver resection and portocaval shunt placement at ten years of age. She presented to our institution in fulminant hepatic failure and was not considered a transplant candidate at that time due to acute illness. In contrast, the 2 patients from our pediatric hospital were both asymptomatic and diagnosed incidentally at 5 months and 1 year, after imaging to evaluate ARPKD. Both children went on to develop CS with congenital hepatic fibrosis, portal hypertension and esophageal varices, eventually undergoing successful liver transplantation at 4 and 13 years old. One patient at our pediatric hospital was transplanted before the development of frank cirrhosis, while the other was transplanted with a cirrhotic liver. Both patients are currently alive and doing well post-transplantation.

Conclusion: Although our case numbers are small, from our emphasis on pathological features, it would appear that consideration for transplantation before the development of severe cirrhosis could eliminate poor outcomes and possibly early death from rapid liver decompensation.

36. Correlation of Endoscopic and Histologic Severity Scores in Pediatric Ulcerative Colitis at First Presentation

A Kovach[1]*, D Moulton*[2]*, W Plummer Jr.*[3]*, W Dupont*[3]*, MC Pacheco*[4]*;* [1]Pathology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee; [2]Gastroenterology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee; [3]Biostatistics, Vanderbilt University, Nashville, Tennessee; [4]Department of Laboratories, Seattle Children's Hospital, Seattle, Washington

Background: In ulcerative colitis (UC), detailed histologic (HIS) scoring systems have been developed for assessment of disease activity and are increasingly being used in the setting of clinical trials. Literature from adult patients has shown correlation between endoscopic (END) and HIS findings at the extremes of disease activity; reproducibility of HIS scores has also been supported. The effectiveness of END appearance at predicting HIS scores in pediatric patients has not been well studied.

Methods: We retrospectively reviewed END images and concurrent H&E-stained biopsies from the distal colon and rectum in untreated pediatric patients at first presentation of UC. END appearance was graded by a pediatric gastroenterologist using the Mayo score (0=normal, 1=mild, 2=moderate, 3=severe). Detailed HIS features were graded independently by two pediatric pathologists using the Geboes score, which uses a 0-to-3-point scale to assess architectural changes, chronic inflammatory infiltrate, lamina propria eosinophilia, lamina propria neutrophilia, epithelial neutrophils, and crypt destruction; a 0-to-4-point scale for erosion/ulceration; and an overall HIS score adding individual scores (total of 22). The HIS scores of the two observers were averaged; in instances of a discrepancy of 2 or more points, the pathologists reviewed the case together and recorded a consensus score. The anatomic site with the higher END score (rectum if the two sites had the same Mayo score) was used for END and HIS score correlation and interpreted using Spearman's rank correlation coefficients. Interobserver agreement of HIS scores, before consensus review of widely differing scores, was assessed by kappa statistics.

Results: Data from 36 patients ages 3-17 years (mean 12, median 13) were available. Average HIS scores were as follows: architecture, 1.6; chronic inflammatory infiltrate, 1.9; lamina propria eosinophilia, 0.7; lamina propria neutrophilia, 1.3; epithelial neutrophils, 1.9; crypt destruction, 1.5; erosion/ulceration, 1.2; and total score, 10.2. The average Mayo score was 2.2. Correlation between END and HIS scores was weakly to moderately positive [Spearman's coefficients 0.15 (lamina propria eosinophilia) to 0.50 (lamina propria neutrophilia), 0.46 for total score]. Similarly, interobserver agreement for HIS scores was weakly to moderately positive [kappa statistics 0.12 (architectural changes and total score) to 0.72 (erosion/ulceration)].

Conclusion: In a cohort of pediatric patients with UC at first presentation, END and HIS scoring systems, developed to assess disease severity in UC of adult patients, show modest positive correlations with one other and with respect to interobserver HIS score assignment. For each HIS parameter, the average score was lower than the average END score. Examination of larger pediatric cohorts, treated patients, correlations of clinical outcomes with individual HIS parameters, and alternate scoring systems may contextualize these findings.

37. Congenital and Non-Congenital Infantile Leukemia Series Comparison

V Knez[1]*, J Schowinsky*[1]*, M Haag*[2]*, B Carstens*[2]*, X Liang*[3]*;* [1]University of Colorado, Aurora, Colorado; [2]Colorado Cytogenetics Laboratory, Aurora, Colorado; [3]Children's Hospital Colorado, Aurora, Colorado

Background: Congenital leukemia, defined as occurring in neonates ≤ 30 days old, is a special category of infantile leukemia in the first year of life which is extremely rare. It is more likely to be of myeloid lineage than lymphoid. In contrast, non-congenital infantile leukemia is

more likely to be lymphoid. Infantile B-ALL is associated with MLL (KMT2A) rearrangements of which t(4;11) is the most common and has the worst prognosis; t(11;19) is the second most common and has a better prognosis. We report 3 cases of congenital B-ALL occurring at our institution over a 30-year period and compare the clinicopathologic features with non-congenital infantile B-ALL.

Methods: Infantile B-ALL cases were reviewed at our institution (1988-2016).

Results: Three cases of congenital B-ALL were identified.

Case 1 was a 1 day old term male delivered by C-section for fetal distress. He had numerous superficial ecchymoses and hepatosplenomegaly. WBC was 600x10^9/L with 94% blasts. The placenta showed numerous blasts that were TdT+CD10-CD34+PAX-5+. Cytogenetics revealed 46,XY,der(6q),del(11q) and FISH detected a MLL rearrangement. The parents chose not to treat the baby. He died 3 days after birth.

Case 2 was a term male whose cord blood was collected for banking. Flow cytometry detected numerous CD34+CD19+ blasts. He was brought to the ER 3 days after birth and a physical exam revealed mild hepatosplenomegaly. WBC was 72x10^9/L with 80% blasts. Flow of the marrow showed TdT+CD19+CD22+CD79a+CD34-CD10- blasts. Cytogenetics revealed 46,XY,t(4;11)(q21;q23) and RT-PCR confirmed MLL-AFF1 fusion. CSF was positive for blasts. Chemotherapy was administered, but at 3 months of age, his leukemia relapsed with a lineage switch to AML. He died of AML and sepsis at 4 months.

Case 3 was a 10 day old term female who had extensive bruising at delivery and received a platelet transfusion. WBC showed 44x10^9/L with 57% blasts. The bone marrow was diffusely replaced by blasts (CD34+TdT+CD10-CD19+CD22+CD79a+). Cytogenetics revealed 46,XY,t(4;11)(q21;q23) and RT-PCR confirmed MLL-AFF1 fusion. Blasts were present in her CSF. She received chemotherapy and is in remission at 7 months of age.

Non-congenital infantile cases consisted of 21 patients (2-11 months old): 52% (11/21) had t(4;11) and 24% (5/21) had t(11;19). Mortality was seen in 39% (7/18). Lineage switch was not observed.

Conclusion: 1. Congenital leukemia can be diagnosed through cord blood or placenta prior to the patients' clinical presentation.

2. Congenital B-ALL appears to have a higher incidence of t(4;11)(q21;q23) (2/3, 67%) and lower incidence of t(11;19)(q23;p13.3) (0/3, 0%) than non-congenital infantile B-ALL (11/21, 52% and 5/21, 24%, respectively) suggesting congenital B-ALL may have a worse outcome. More data is needed to verify this hypothesis.

38. ALK+ Histiocytosis: Two Atypical Presentations in an Already Atypical Disease

D Olson[1]*, C Galambos*[1]*, V Savell*[2]*, X Liang*[1]*;*
[1]University of Colorado Denver/Children's Hospital Colorado, Aurora, Colorado; [2]Driscoll Children's Hospital, Corpus Christi, Texas

Background: The *ALK* gene is an oncogene implicated in tumorigenesis of lymphomas, lung cancer, neuroblastoma, and inflammatory myofibroblastic tumor. More recently, *ALK* fusions have been identified in the histiocytic lesions Erdheim-Chester disease and ALK+ histiocytosis. Only 3 cases of ALK+ histiocytosis have been described in the literature, all occurring in the livers of infants. We describe 2 patients with atypical histiocytic proliferations with ALK expression in the lung and skin to further expand the current perception and knowledge of ALK+ histiocytosis.

Methods: Histologic review with special studies and clinicopathologic correlation of 2 cases.

Results: Case 1 is a male with a neonatal history significant for prolonged oxygen requirements and anemia and thrombocytopenia requiring transfusions. By 7 months, he no longer required oxygen; however, CT scans from the neonatal period to one year of age progressed from diffuse hazy interstitial opacities to reticular opacities with septal thickening and nodularity. At 11 months, lung biopsy showed marked septal and pleural fibrosis associated with atypical histiocytes

(CD1a-, CD68+, CD163+, S100-, ALK1+), *ALK* rearrangement negative and bone marrow (BM) negative. He is currently stable without medication or oxygen, but CT scan at 14 months remains unchanged.
Case 2 was a finger mass from a 9-year-old male present for one year. Sections showed large atypical histiocytes infiltrating soft tissue (CD1a-, CD68+, CD163+, S100-, ALK1+), *ALK* rearrangement positive. The patient was lost for follow up.
Three cases from the literature for comparison (Chan, et al, Blood 2008): All females aged from neonate to 3 months. The primary lesions were all in the liver (CD1a-, CD68+, CD163+, S100+, ALK1+) with BM involvement in 2 cases and *ALK* rearrangement in 1 case. The disease slowly resolved over many months in all patients with 2 of them having received chemotherapy.
Conclusion: 1. Histiocytic lesions can be diagnostically challenging and their classification continues to evolve as advanced diagnostic techniques are applied. ALK+ histiocytosis should be considered in any patient presenting with an atypical histiocytic proliferation that cannot be readily classified.
2. The two cases we present suggest this rare entity can be found outside of the infantile period and may not be primarily in the liver. Its clinical presentation and immunophenotypic features are more variable than previously thought.
3. S100 expression is present in hepatic lesions but not in extra-hepatic lesions. Its significance is unclear presently.
4. The biological behavior in the long term remains uncertain. The presence of ALK expression may be important to identify as ALK tyrosine kinase inhibitors are available should future cases require additional therapies.

39. Clonal Link between Acute Myelomonocytic Leukemia and a Low-Grade Histiocytic Cerebral Mass

D Olson*[1]*, M Lovell*[1]*, X Liang*[1]*, J Picarsic*[2]*, K Swisshelm*[3]*, C Galambos*[1]*; [1]University of Colorado Denver/Children's Hospital Colorado, Aurora, Colorado; [2]University of Pittsburgh/Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania; [3]University of Colorado/Colorado Genetics Laboratory, Aurora, Colorado

Background: The most recent Histiocyte Society classification includes a category of histiocytic malignancies secondary to a hematopoietic neoplasm (HN). Shared clonal relationships between these lesions have been confirmed in many cases with a common molecular signature despite their histologic divergence. This classification does not include a category of low-grade secondary histiocytic lesions (HL), but they have been described following acute lymphoblastic leukemia and juvenile myelomonocytic leukemia. These lesions present a diagnostic dilemma and a management challenge for clinicians as some have shown aggressive behavior despite a low-grade histologic appearance. We describe the first reported case of a low-grade HL following acute myeloid leukemia (AML) with a shared molecular signature to bring awareness of these uncommon entities.
Methods: Histologic review with special studies and clinicopathologic correlation of 1 case.
Results: A 7-month-old male presented with AML with inv(16) (CBFB rearrangement) and CSF involvement. He responded to chemotherapy with remission until presenting at 38 months with neurological symptoms. Bone marrow biopsy and molecular analysis were negative for recurrent AML. MRI showed two distinct thalamic and parietal masses. The thalamic mass was diagnosed as diffuse midline glioma with H3 K27M and BRAF V600E mutations and negative for CBFB rearrangement. The parietal mass showed a low-grade HL with cytologic features reminiscent of juvenile xanthogranuloma

(CD68+, CD163+, Fascin+, CD14+, Factor XIIIa variably +, CD1a-, S100-, MPO-) . A demyelinating process was ruled out and a low MIB-1 rate (less than 10%) ruled against a high grade (myelomonocytic) process. FISH and RT-PCR identified the CBFB rearrangement identical to that of the original AML and no H3 K27M or BRAF V600E mutations were detected. A diagnosis of an atypical low-grade HL with inv(16) following AML was made. Testing for a cancer predisposition syndrome has been negative. One year post-surgical excision of both masses the patient is alive with partial response to vinblastine and vemurafenib for the midline glioma. Recent imaging shows no progression in either cerebral tumor site, and his AML remains in remission.

Conclusion: HL developing after or concurrent with a separate HN should be assessed for a possible shared molecular signature. These lesions may represent a transdifferentiation from the original HN and may share a common hematopoietic precursor. The uncertain biological behavior of these low-grade HLs warrants an interdisciplinary clinical approach and focused research to understand the role of the shared molecular signature in the development and biological behavior of these HLs.