2021 SPP Virtual Spring Meeting

Abstract Book

Platform I: Pediatric - Molecular and Dermpath
Friday, March 12
12:30pm - 12:45pm ET

01

High-Depth Tissue-Based Testing for Molecular Diagnosis of Disorders of Somatic Mosaicism

S Sen[1], *J Reuther*[1], *M Eldomery*[1], *H Voicu*[1], *P Mahajan*[1], *H Helber*[1], *T Phung*[1], *M Tam*[2], *C Renee Webb*[2], *V Reid Sutton*[1], *J Margolin*[1], *R Venkatramani*[1], *K Patel*[1], *N Quintanilla*[1], *D Lopez-Terrada*[1], *K Fisher*[1], *I Iacobas*[1], *A Roy*[1]; [1]Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; [2]Texas Children's Hospital, Houston, Texas

Background: Disorders of somatic mosaicism, a clinically heterogeneous group of syndromic and non-syndromic conditions are characterized by post-zygotic mosaicism for genetic variants in affected tissues. While laboratory testing guidelines for somatic mosaic disorders are yet to be established, tissue-based next-generation sequencing (NGS) has emerged as a high-sensitivity method for detecting pathogenic variants in these disorders. We report the diagnostic yield of high-depth tissue-based NGS on 37 consecutive cases at a pediatric hospital using an existing tumor pipeline.

Methods: Patients with a somatic mosaic syndromic diagnosis ('CLOVES', Klippel-Trenaunay', 'MCAP', etc.) or clinical features of somatic mosaic disorders ('overgrowth', 'vascular'/'venous'/'lymphatic malformation', etc.) with NGS testing were identified, following IRB approval. After histopathologic review, NGS was performed on affected tissue (35 FFPE, 2 fresh) with a 124-gene panel at 500-1000x coverage and analyzed using a modified pipeline for low variant allele fractions (VAF) with orthogonal confirmation. Variants were classified as tier I-IV based on professional guidelines.

Results: Thirty-seven (16 male, 21 female; age: 1-24 years) patients were identified (2018-2020). Tissue-based NGS testing detected a tier I/II pathogenic variant in 17/37 (45.9%) patients, including in *PIK3CA* (8x), *KRAS* (2x), *GNAQ* (2x), *GNAS*, *GNA11*, *NRAS*, *AKT1*, *PTEN*, and in 1 case both a *PIK3CA* and *GNAQ* variant. Pathogenic variants were identified in 10/17 (58.8%) syndromic and 7/20 (35%) non-syndromic patients. Median VAF was low at 8.6% (4-80%) with 10/18 detected at <10%. While 15/18 tier I/II variants were classic hotspot mutations (*PIK3CA* H1047R, E542K, E545K; *KRAS* G12D; *GNAQ* R183Q, Q209L; *GNAS* R201H; *GNA11* Q209P; *NRAS* Q61R; *AKT1* E17K), less common pathogenic variants (*PIK3CA* C604R, T1025A; *PTEN* Q110X) were also identified. Importantly, tissue NGS testing detected a pathogenic variant in 4/10 patients with prior non-informative genetic tests on blood (clinical exomes, overgrowth panels, single gene tests). Unexpected findings included the Proteus syndrome associated *AKT1* E17K mutation in an individual with clinical features of CLOVES syndrome, and a *PIK3CA* H1047R mutation in a laryngeal hamartoma. Detection of targetable mutations resulted in enrollment of 6 patients on therapeutic clinical trials with targeted inhibitors and counseling for prognosis.

Conclusion: Tissue-based NGS detected a broad range of variants of established diagnostic and therapeutic significance in this cohort, including in unresolved cases with germline testing. Detection of actionable mutations directly impacted clinical management. Evaluation of larger cohorts and long-term outcome studies will help establish the clinical utility of such diagnostic testing.

Platform I: Pediatric - Molecular and Dermpath
Friday, March 12
12:45pm - 1:00pm ET

02

Constitutional Mismatch Repair Deficiency: A Report of Five Patients

S Logan[1], *J Vazzano[2], B Wilkins[3], M Duvall[4], S MacFarland[3], M Conces[1], D Boué[1], C Pierson[1], S Kahwash[1], K Schieffer[1], C Cottrell[1], S Colace[1], S Erdman[1], K Zajo[1], A Shenoy[1];*
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Background: The mismatch repair (MMR) system eliminates single-base mismatches and insertion-deletion loops that arise during DNA replication. Constitutional MMR deficiency (CMMRD) results from homozygous or compound heterozygous mutations of one or more MMR genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*), or rarely, in a gene called *EPCAM*, in contrast to the monoallelic germline alterations implicated in most cases of Lynch Syndrome (LS). In addition, while tumors in LS usually arise in the third decade of life or later, CMMRD often manifests within the first or second decades.

Methods: Patients carrying homozygous or compound heterozygous mutations in MMR genes were identified in the archives from two institutions. Clinicopathologic features of each patient, including family history, were recorded.

Results: Five cases of CMMRD were identified, each demonstrating alterations in *MSH6* (homozygous: N = 3, compound heterozygous: N = 1) or *PMS2* (homozygous, N = 1). The average age at presentation was 8 years (range: 2-12 years) and four of the five patients were male. Café-au-lait spots were seen in all five patients, and two patients showed additional findings typically associated with neurofibromatosis type 1 (NF1) (e.g., Lisch nodules, optic glioma, axillary freckling). One patient with *MSH6* alteration showed concomitant dextrocardia and primary ciliary dyskinesia. In contrast to colonic or endometrial cancers as the most common presenting tumors in LS, high-grade glial/glioneuronal neoplasms and lymphoblastic lymphomas were the most common tumors among these five patients with CMMRD. Three patients also developed gastrointestinal neoplasia, diagnosed as colonic adenocarcinoma in one patient with *MSH6* mutations, and tubular adenomas in two patients: one with *MSH6* and the other with *PMS2* mutation. Three patients harboring *MSH6* mutations are deceased (mean duration of survival after diagnosis of first malignancy: 3 years; range: 1 to 6 years), one with *MSH6* mutations is alive with malignancy (1 year following diagnosis of first malignancy), and the patient with *PMS2* alteration is alive with no evidence of malignancy (13 years following diagnosis of first malignancy).

Conclusion: The presence of NF1-associated clinical features among these patients with CMMRD is diverse and can involve multiple organ systems. Importantly, the presence of NF-1-like features with negative genetic testing for *NF1* mutations should raise suspicion for other diseases such as CMMRD.

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03

MYOD1 L122R Mutations in Pediatric Rhabdomyosarcoma

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Background: Embryonal rhabdomyosarcoma (ERMS) is a clinically and genetically heterogeneous neoplasm that is associated with variable prognosis. The spindle cell/sclerosing variant (SRMS) has emerged as a separate entity and was recently found to harbor *MYOD1* gene mutations in a subset of adult cases.

Methods: To explore the MyoD1 mutation status in pediatric rhabdomyosarcoma and highlight its relationship to MyoD1 protein expression, we analyzed a total of 37 non-alveolar RMS (0-35 years, median age 5 years) for *MYOD1* Leu122Arg (L122R) mutations in correlation with clinical data and MyoD1 expression by immunohistochemistry.

Results: DNA was successfully isolated from formalin-fixed paraffin-embedded tissue and processed for Sanger sequencing. *MYOD1* L122R mutations were found in three cases (8%), comprising only 6.5% (2/31) of the pediatric population (<18 years old); two were heterozygous and one was homozygous for the mutation. The positive cases included 2/13 (15%) SRMS and 1/24 ERMS. MyoD1 staining did not exhibit any correlation with the mutation status as two cases were negative and one had focal positive (<50%) staining. The ERMS with the heterozygous-mutation was located in the endocervix of an 11-month old female infant who presented with a protruding vaginal mass that was classified as botryoid RMS. This patient was alive, healthy and relapse-free after 72-month follow-up. The SRMS tumor with heterozygous mutation was in the parotid gland of a 12-year old female who died of recurrent disease. The SRMS tumor with homozygous mutation was located in the paraspinal soft tissue of a 35-year old man who did not have further follow-up information. Both SRMS cases were of the spindle cell variant which was the predominant subtype in our study.

Conclusion: *MYOD1* L122R mutations were infrequent in our series of pediatric RMS, occurred both in SRMS and ERMS, did not correlate with MyoD1 staining, and were not uniformly associated with poor prognosis.

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04

H3K27 Trimethylation Status of DICER1-Associated Tumors

M Alturkustani[1], *C Bockoven[1], R Mahabir[1], N Shillingford[1], R Schmidt[1], S Zhou[1], M Warren[1], B Pawel[1], L Wang[1];* [1]Children's Hospital Los Angeles, Los Angeles, California

Background: DICER1-associated tumors are heterogenous and affect many organs. DICER1-associated primary intracranial sarcoma is associated with H3K27me3 loss by immunohistochemistry. However, the H3K27me3 status in other DICER1-associated tumors is still unknown.

Methods: Cases with confirmed *DICER1* mutations (sporadic and germline) or with diagnosis of pleuropulmonary blastoma (PPB) were retrieved from our database. A representative section from each tumor was stained with anti-H3K27me3 antibody. The related clinicopathological and molecular features were reviewed.

Results: Fifteen tumors from 14 patients were included. We found that H3K27me3 expression was heterogenously reduced/lost in a subset of Sertoli cells in 3/5 cases of intermediately to poorly differentiated Sertoli-Leydig cell tumors with heterologous elements. One intracranial sarcoma showed complete loss of H3K27me3 in the sarcomatous spindle cell component while another intracranial sarcoma showed partial loss. Four cases of type II PPB (2 with *DICER* mutations, and 2 with unknown *DICER* status) and a single case of type III PPB (unknown *DICER* status) showed similar heterogenous loss of H3K27me3 staining restricted to the spindle cell component. All other components, including Leydig cells and areas of epithelial, cartilaginous and rhabdomyomatous differentiation in these tumors and all cells of the remaining 3 cases (one papillary thyroid carcinoma and two cases of PPB type I including one with germline *DICER* variant) demonstrated retained H3K27me3 staining.

Conclusion: H3K27me3 loss in DICER1-associated tumors is heterogenous and restricted to subsets of neoplastic cells. The cells with H3K27me3 loss were predominately seen in atypical spindle cells of PPBs and intracranial sarcomas, and poorly differentiated Sertoli cells in the Sertoli-Leydig cell tumors. This staining pattern may be a reflection of epigenetic changes in DICER1-associated tumors.

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05

ALK-Rearrangements in IFS-like Pediatric Spindle Cell Tumors

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Background: Recurrent gene alterations in receptor tyrosine kinase (RTK) and downstream effectors are described in infantile fibrosarcoma (IFS)/cellular congenital mesoblastic nephroma (cCMN) and a subset of spindle cell sarcomas provisionally designated "*NTRK*-rearranged" spindle cell tumors with variable CD34/S100 expression. These tumors demonstrate overlapping morphologies and harbor fusions in *NTRK1/2/3*, *RET*, *MET*, *RAF1*, and *BRAF*. The relationship between IFS/cCMN and the provisional entity is not fully elucidated.

Two published case reports in adults each highlight a single case harboring ALK-fusion with CD34/S100 co-expression. Herein we describe a cohort of tumors with IFS-like morphology and *ALK*-fusions, expanding the spectrum of RTK-alterations found in this emerging diagnostic entity. Knowledge of potential genetic alterations in this spectrum of tumors is key for diagnostic and targeted therapeutic purposes.

Methods: This study was approved by Institutional Review Boards of participating institutions. Five *ALK*-rearranged pediatric mesenchymal neoplasms with features not typical of inflammatory myofibroblastic tumor were encountered in routine clinical practice from 3 institutions. Clinicopathologic features were assessed. All underwent partner agnostic targeted RNA sequencing on clinically validated platforms.

Results: Tumors occurred in patients 3 months to 10 years (median 24 months), 3:2 M:F ratio, with average size of 7.7 cm. Three tumors were in soft tissue and 2 in the kidney. *ALK* fusions were present in all tumors, including 2 novel partners. Clinicopathologic features are summarized in the table. Morphologic features included spindle cells arranged in long fascicles, haphazard primitive ovoid cells within a myxoid to collagenized stroma, areas of dense sclerosis/hyalinization, and/or prominent perivascular hyalinosis. Some tumors showed intratumoral heterogeneity.

Patien	Age (yrs)	Location	Size (cm)	ALK fusion partner	IHC			
					CD34	S10	SMA	AL
1	0.25	paraspina	5.3	*LRRIP1*	patch	-	-	+
2	2	hand	5.8	*ERC1*	rare	-	-	+
3	2	kidney	9.3	*TMP3*	-	-	-	NA
4	10	kidney	14	*CLIP1*	patch	+	patch	+
5	2	scalp	4.3	*AK5*	-	rare	-	NA

Conclusion: We present the first series of *ALK*-rearrangements in IFS-like pediatric tumors. Notably, 2 were located in the kidney representing cCMN, including 1 with robust co-expression of CD34/S100. Our series expands the spectrum of RTK-rearranged tumors and reinforces the compelling overlap between IFS/cCMN-like tumors and the provisional entity of "*NTRK*-rearranged spindle cell tumors."

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06

Pediatric PLAG1-Rearranged Fibroblastic/Fibromyxoid Tumors: A Novel Entity or Morphologic Spectrum of Lipoblastoma

S Bannoura[1], *J Putra[1], H Chen[1], B Ngan[1], G Somers[1], R Chami[1];* [1]The Hospital for Sick Children, Toronto

Background: Fibroblastic soft tissue tumors (FSTTs) are a heterogeneous group of lesions that range from reactive entities to frank malignancies. Due to overlapping histologic features and lack of specific immunomarkers, accurate diagnosis and clinical management remain challenging. We performed molecular analysis to determine whether genetic abnormalities can help better define these tumors. Herein, we describe four cases of pediatric FSTTs not fitting into any specific WHO category that harbored *PLAG1* fusion transcripts.

Methods: Soft tissue tumors diagnosed as fibroblastic neoplasm (NOS), low-grade, during the last two years at our institute were reviewed. Age, gender, site, and size were documented. Histopathology and immunohistochemistry were reviewed, and molecular analyses using the TruSight RNA-Seq panel & additional immunomarkers were performed. FSTTs showing *PLAG1* rearrangements were included in the study.

Results: Two cases showed biphasic histology of myxoid and fibroblastic areas. Both components were positive for CD34 and desmin, and myxoid areas also expressed S-100 protein. The third case consisted mainly of spindled cells embedded in fibrous stroma, and rare myxoid nodules. Desmin was expressed in both components, and myxoid zones were positive for CD34 and S100. The fourth case consisted only of spindled cells scattered in a collagenous stroma, and showed only patchy positivity for CD34 and desmin. All cases were well-defined, unencapsulated, and cytologically bland without necrosis and with low proliferation index. None showed adipocyte differentiation. All cases were negative for SMA, myogenin, AE1/AE3, EMA, MUC4, STAT6, B-catenin, pan-TRK, and SOX10. Resections margins were negative. Sites included extremity (2), neck (1) and back (1). Tumor sizes varied from 2.5 to 7.1 cm. Ages (1 female & 3 males) ranged from 2 to 9 years old. Cases 1 & 4 showed *YWHAZ-PLAG1* & *CHCHD7-PLAG1* fusions, case 2 showed *PLAG1-BOC* fusion, and case 3 showed *MEG3-PLAG1* fusion. All four cases showed diffuse PLAG1 immunopositivity.

Conclusion: We report four cases of pediatric *PLAG-1*-rearranged fibroblastic/fibromyxoid tumour with variable positivity for CD34 and desmin. RNA-seq detected four *PLAG1* fusion partners, of which three were known (*YWHAZ, CHCHD7* & *BOC*) and one was novel (*MEG3*). None of our cases showed features typical of lipoblastoma (three of four excisional biopsies were entirely submitted for microscopic examination). We believe our cases represent a distinct non-lipoblastic pediatric FSTT. Three cases were recently diagnosed and have no significant follow-up; one case had no recurrence after 2 yrs.

Platform I: Pediatric - Molecular and Dermpath
Friday, March 12
2:00pm - 2:15pm ET

07

The Conundrum of Spitzoid Lesions in Childhood: Patterns, Pitfalls & Lessons Learned

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Background: A melanocytic neoplasm of either epithelioid or spindle cells, Spitz nevi (SN) generally appear in childhood with a predilection for the head and neck. Occasionally the lesions are not "classic" SN, nor do they fulfil criteria for melanoma. The term "Spitzoid lesion/tumor' (SL) is often applied. Retained p16 staining usually excludes melanoma while genomic instability is supportive of melanoma. We reviewed 16 cases of SN/SL over a 5 year period to better understand the variable histology and any patterns of cell growth.

Methods: Institutional records were queried for patients with a clinical diagnosis of "SN" or "SL" from January 2015 to December 2019. The clinical history, pathology and expert consultation reports, when available, of 16 cases were reviewed. When available immunohistochemical stains (p16 and ALK) and molecular diagnostic results were reviewed.

Results: Sixteen patients were identified (M: 9, F: 7), aged 1 to 20 years at diagnosis. All had clinical diagnoses of "SN". The head and neck was most commonly involved site (n=8, including cheek-4, ear-2, lip-1 and temple-1); others included arm, thigh, knee and forearm.

Frequent histologic features included acanthotic epithelium, perijunctional edema, spindled and polygonal melanocytes in the dermoepidermal junction. Expansile nests in the papillary dermis were also common as were Kamino bodies. The dermis may be sclerotic and inflamed. Histopathology varied, with 5/16 patients showing *compound SN*, 2/16 *atypical SL*, 3/16 *SN*, 2/16 *Desmoplastic SN*, 2/16 *Pagetoid SN,* 1/16 *SL with associated kinase gene fusion*, and 1/16 with a *Spitzoid melanoma*. ALK immunostain was performed on 5 cases, and negative in 3 and positive in 2; p16 was done on 4 cases, was positive in 3 with complete loss of expression in 1. One patient had p16 expression with chromosome 9 loss on array based comparative genomic hybridization (aCGH). The lesion of the 5 year-old with Spitzoid melanoma was exophytic, with polypoid proliferation of enlarged cells, and expansion of lesional cells into fat lobules. The lesional cells were ALK negative and retained p16 staining although aCGH revealed gain in chromosome 2q with a loss in chromosomes 1p, 2p, 3p, and 9.

Conclusion: While typical SN are easily recognized, unusual features such as pagetoid scatter and, multinucleated melanocytes may be seen in otherwise benign SN/SL. Kinase gene fusion, a common mechanism of induction of SN/SL, makes ALK staining useful. Retained p16 (encoded in CDKN2A, chromosome 9p) staining is supportive of SL/SN and not melanoma. However this is a pitfall and can be potentially misleading. Therefore, aCGH is critical to identifying chromosomal gains & losses that indicate genomic instability, and therefore predict behavior similar to melanoma.

Platform I: Pediatric - Molecular and Dermpath
Friday, March 12
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08

KRAS Mutations are Commonly Found Throughout Type 1 Congenital Pulmonary Airway Malformations

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Background: The etiology of type 1 congenital pulmonary airway malformations (CPAMs) remains unclear; however recent studies have reported *KRAS* mutations in type 1 CPAMs and associated mucinous cell clusters (MCCs). Rare cases of metastatic mucinous adenocarcinoma arising in type 1 CPAMs have been reported in the literature, suggesting that *KRAS* mutations may underlie potential malignant behavior. We aimed to characterize the landscape of *KRAS* mutations in a large cohort of type 1 CPAMs, determine the heterogeneity of *KRAS* mutations within each individual, and to use our next generation sequencing (NGS) panel to determine if there are additional oncogenic mutations present.

Methods: Regions of interest were enriched via macrodissection of FFPE sections, with each MCC macrodissected from a different block to prevent cross contamination. DNA was isolated and exon 2 of KRAS was amplified using primers designed to detect mutations with allele frequency of ≥5%. PCR products were Sanger sequenced, and analyzed using Mutation Surveyor (SoftGenetics, PA).

MCCs with sufficient DNA quantity and quality were evaluated using our 238 gene NGS panel which covers all exons, 10 bp of flanking intronic sequences, and selected intronic mutations using custom-designed RNA probes (SureDesign, Agilent Technologies, CA). Copy number variation (CNV) was analyzed using probes targeting common SNPs. Following DNA extraction and library preparation, samples were sequenced on a HiSeq platform using 150 bp paired-end sequencing (Illumina, CA). Data were analyzed using ConcordS v2 (SNVs and indels, lab developed) and NextGENe v2 (CNVs; SoftGenetics).

Results: We sequenced 61 MCCs from 18 infants with type 1 CPAMs, with an average of 3.4 MCCs per patient (range 1-10). *KRAS* mutations were found in all MCCs, and in each individual patient the same *KRAS* mutation was detected in every MCC. Furthermore, the non-mucinous CPAM tissue always contained the same *KRAS* mutation (n= 15) while the adjacent normal lung tissue was wild type (n=9).

We also identified *KRAS* mutations in 7 of 9 type 1 CPAMs with no identifiable MCCs on H&E. In total, we have identified *KRAS* mutations in 31 out of 33 type 1 CPAMs. The most common *KRAS* mutations were p.12G>D (n=19, 61%) and p.12G>V (n=11, 35%). A *KRAS* p.12G>R mutation was detected in 1 patient.

NGS was performed on MCCs from 7 different patients, and did not identify any CNVS or additional disease associated variants.

Conclusion: We have identified *KRAS* mutations in 94% of type 1 CPAMS (31/33 patients), and for any given patient the same mutation was found in all tested MCCs and non-mucinous CPAM tissue but not normal lung tissue. These findings suggest that mosaic *KRAS*

mutations may be a key feature of type 1 CPAMs, and that additional oncogenic driver mutations are uncommon within MCCs.

Platform I: Pediatric - Molecular and Dermpath
Friday, March 12
2:30pm - 2:45pm ET

09

The Spectrum of Meningothelial Hamartoma-Meningoencephalocele: A Pitfall in Pediatric Dermatopathology.

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Background: Meningothelial hamartomas (MH) and meningoencephaloceles (MEC) comprise a spectrum of malformations occurring in relatively young children, which frequently represent a diagnostic challenge in pediatric dermatopathology. We describe four cases of lesions within the cutaneous meningothelial hamartoma – meningoencephalocele spectrum, detailing their clinical and histologic features, and reviewing their differential diagnoses.

Methods: Four cases of MH/MEC were identified from four different institutions around the world. Their clinical and histological features, including immunophenotypes were recorded and compared.

Results: Clinical findings are summarized in table 1:

Origin	Age	Size	Sex	Location in scalp	Clinical impression
Argentina	4 years	0.7 x 0.3 cm	M	Occipital	Congenital asymptomatic nodule
USA	7 years	2.5 x 2.5 cm	F	Parieto-occipital paramedian	Aplasia cutis
Russia	18 months	1.5 x 1.5 cm	F	Posterior parieto-occipital	Dermoid cyst
Russia	28 months	1 x 1 cm	F	Posterior parietal	Dermoid cyst

Histologically, in all cases we found central epidermal atrophy with adnexal loss and underlying dermal nests of EMA+ meningothelial rests. In two cases, there were also foci of S100+ Schwannian tissues, and GFAP+ glial elements, confirming the presence of encephalocele components. One case had also melanin-containing cells (raising the possibility of a neurocristic hamartoma), but those cells were later interpreted as consistent with melanophages. Adjacent and deeper areas showed dermal replacement with fibrosis and focal penetration into subcutaneous tissue. A wide histologic differential diagnosis includes neurocristic hamartoma, aplasia cutis, and less likely, melanotic neurofibroma, pigmented dermatofibrosarcoma, desmoplastic malignant melanoma, scar tissue, and other skin tumors (cellular neurothekeomas and fibrous histiocytoma). When vascularity is prominent, lymphatic or blood vascular proliferations should be ruled out.

Conclusion: As expected in a neural crest-derived spectrum of lesions, MH-MEC reproduce the wide variety of differentiation phenotypes related to their origin. They can be separated

from a relatively large number of differential diagnoses if one takes into account the immunophenotype and developmental implications of these lesions.

Platform II: Pediatric - GI
Saturday, March 13
10:30am - 10:45am ET

10

Histopathologic Characteristics of Pediatric PSC-IBD: A Distinct Clinicopathologic Group

J Putra*[1]*, R Little*[1]*, B Kamath*[1]*, A Griffiths*[1]*, A Ricciuto*[1]*, I Siddiqui*[1]*; [1]The Hospital for Sick Children, Toronto

Background: Eighty percent of pediatric patients with primary sclerosing cholangitis (PSC) have underlying inflammatory bowel disease (IBD), usually with a distinct clinical phenotype (PSC-IBD). The predominance of colitis with greater right-sided activity endoscopically is characteristic, but histologic findings have not been critically examined. We aimed to delineate the histologic phenotype of pediatric PSC-IBD.

Methods: Fifty PSC-IBD patients (66% male) underwent ileocolonoscopy at time of IBD diagnosis (median age 13.2 years), when disease activity (measured by Pediatric Ulcerative Colitis Activity Index/PUCAI) was remission/mild/moderate/severe in 16%/56%/26%/2%, while Mayo endoscopic scores were quiescent/mild/ moderate/ severe in 8%/34%/46%/12%. Two pediatric GI pathologists independently reviewed pre-treatment mucosal biopsies to assess histologic activity and presence/absence of individual features associated with IBD. Inter-rater reliability of individual signs of inflammation and of the Nancy Index (NI) in right and left colon were assessed using, respectively, Fleiss' Kappa and intra-class correlation coefficient (ICC) with 95% confidence intervals. Construct validity of the NI in PSC-IBD was assessed using global endoscopic severity (GES) as gold standard. Spearman correlations were used to determine which specific histological descriptors best correlated with GES.

Results: Histologically, pancolitis was present in 42 (84%), and backwash ileitis in 26 (53%) patients. Inflammation was right side predominant in 48%, left side predominant in 16% and similar throughout the colon in 36%. Rectal histology was normal in 6%. Right NI mean was 2.1 (SD 0.78), range 0-4, comparable to the left colon NI (mean 2.1, SD 0.76, range 0-4). NI inter-rater reliability was very high (ICC 0.94, 95% CI 0.90-0.97 right colon; ICC 0.96, 95% CI 0.94-0.98 left colon). The right and left colon NI were weakly correlated with each other ($r=0.38$, $p=0.01$). Right and left NI correlated poorly with clinical activity represented by PUCAI score ($r=0.12$-0.13, $p>0.05$). The left NI correlated moderately with GES ($r=0.61$, $p<0.001$), while the right NI correlated less well with GES ($r=0.38$, $p=0.01$). Chronic inflammation correlated more strongly than markers of acute inflammation with GES in the right ($r=0.54$, $p<0.001$) and left ($r=0.61$, $p<0.001$) colon.

Conclusion: The unique macroscopic phenotype of PSC-IBD with pancolitis, backwash ileitis and frequent right-sided predominance was observed at a histologic level in our pediatric cohort. The NI correlates moderately with GES in PSC-IBD but poorly with PUCAI, in keeping with the concept that clinical activity is a poor marker of mucosal inflammation in PSC-IBD.

Platform II: Pediatric - GI
Saturday, March 13
10:45am - 11:00am ET

11

Consensus in the Assessment of Lamina Propria Fibrosis in Eosinophilic Esophagitis

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Background: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease associated with atopy. Well-established criteria for the histologic diagnosis of EoE includes peak eosinophils per high power field in esophageal epithelium. Recently there has been an interest worldwide and at our institution regarding whether lamina propria (LP) fibrosis, another common finding in EoE, may portend fibrostenotic complications and warrants consistent sampling of subepithelial tissue during endoscopy. Unfortunately, inconsistency in the histologic diagnosis and reporting of LP fibrosis has limited the study of the clinical and prognostic significance of this finding. As a quality improvement project, we sought to measure the degree of consensus in the diagnosis of LP fibrosis amongst our pediatric pathology group to inform a future educational intervention to improve our practice.

Methods: The study authors selected 25 de-identified whole slide image cases of EoE with adequate LP and no fibrosis (n=10), adequate LP and fibrosis (n=9), and inadequate LP for evaluation (such as due to crush artifact or obscuring lymphocytes) (n=6); the study authors categorized the cases by blinded review with unanimous or majority agreement (2 of 3). Staff pediatric pathologists (n=8) separate from the study authors were asked to classify each biopsy into one of eight diagnoses that assessed the adequacy of LP and severity of fibrosis. Consensus was defined as >70% agreement (6/8).

Results: In this survey, 64% (16 of 25) of the cases reached consensus in the general categories of no fibrosis (n=3), fibrosis (n=7), or inadequate LP (n=6). Two cases reached consensus but disagreed with the study authors' designation (one designated as 'no fibrosis' but achieving consensus for 'fibrosis' and one designated 'no fibrosis' but achieving consensus for 'inadequate'). Analysis of the 9 cases lacking consensus reflected disagreement over LP adequacy (n=7) and mild versus no fibrosis (n=2).

Conclusion: Evaluation for histologic lamina propria fibrosis in eosinophilic esophagitis is challenging. We document moderate consensus in the assessment of esophageal LP fibrosis in a large pediatric pathologist group, representing one of the first studies to prospectively analyze pathologist performance and consensus in this area. An educational intervention to improve consensus should include clearer definitions of LP adequacy, fibrosis, and pitfalls in interpretation. Such an intervention is likely to benefit patient care and future clinicopathologic correlation studies in EoE.

Platform II: Pediatric - GI
Saturday, March 13
11:00am - 11:15am ET

12

Evaluating the Prognostic Implication of Collins Histology Scoring System in a Paediatric Population of Eastern Ontario with Eosinophilic Esophagitis (EoE)

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Background: The 2016 Histology Scoring System (HSS) was developed by Collins et al as a robust measure, evaluating the grade and stage of multiple endoscopic parameters and peak eosinophilic count in patients with EoE. The aim of this study was to apply the Collins HSS at The Children's Hospital of Eastern Ontario (CHEO) in Canada to determine if the HSS can better detect endoscopic and symptom improvement compared to the CHEO traditional histologic system.

Methods: Between 2014-2016, a retrospective chart review of patients' electronic medical records (EMRs) was performed. All patients ≤ 18 years old with a clinical, endoscopic, and histological diagnosis of EoE and whose records included initial and follow-up upper gastrointestinal (GI) endoscopies and esophageal biopsies, were included. Patients with syndromic conditions, history of any other GI disease, and use of medication at the time of initial presentation and/or endoscopy, were excluded. Two pediatric pathologists and one pathology resident assessed the esophageal biopsies using the new HSS (8 parameters; each (0-4 scale) for both grade and stage, and the CHEO system (peak eosinophil count). Final grade and stage scores were obtained by summing the scores across the 8 endoscopic parameters for each esophageal location. The Area Under the Curve (AUC) evaluated the diagnostic performance of the CHEO and HSS scoring system to predict endoscopic and symptom improvement. A ROC test was used to evaluate the difference in the AUCs of the two systems. All statistics were computed using R Version 4.0.3.

Results: A total of 40 patients were included in the study, of which 27 (75%) were male. Main symptoms at initial presentation included: food impaction [n=9, 22.5%] and dysphagia [n=10, 25%]. Thirty-five (87.5%) patients demonstrated symptom- and twenty-five (62.5%) endoscopic improvement at follow-up. In the proximal section of the esophagus, the HSS system outperformed the CHEO system in predicting endoscopic improvement by 16.8% when examining the change in grade [AUC=65.6%; 95% CI: (47.6%; 83.6%) vs 48.8%; (30.2%, 67.4%); p=0.01], and 17.1%, when examining the change in stage scores [AUC 65.9%; CI (48.6%, 83.2%) vs 48.8% (30.2%, 67.4%); p= 0.0.02]. Although not statistically significant, the HSS system outperformed the CHEO system in detecting symptom improvement at each site of the esophagus, with greatest percent difference (14.2%) in the mid esophageal section, when examining change in stage scores [AUC 63.1% (36.6%, 89.7%) vs 48.9% (10.96%, 86.8%)].

Conclusion: At our institution, adoption of the HSS in assessing biopsies of EoE patients might be warranted; our data suggested it might be superior in detecting endoscopic and symptom improvement compared to the CHEO system. A bigger sample size may give robust differences in all locations.

Platform II: Pediatric - GI
Saturday, March 13
11:15am - 11:30am ET

13

Histopathologic Patterns of Liver Injury in Congenital Hepatitis B: A Retrospective Review

A Shukri[1], *B Fung[1], V Prasad[1], M Conces[1], S Mangray[1], A Shenoy[1];* [1]Nationwide Childrens Hospotal, Columbus, Ohio

Background: Patterns of hepatic injury in chronic hepatitis B have been extensively studied within adult liver. However, the morphologic patterns of injury within immature liver are not well described. We performed a retrospective clinicopathologic review of the histopathologic patterns of liver injury in cases of congenital/perinatally acquired hepatitis B on liver needle core biopsies.

Methods: Institutional records were queried for liver biopsies in patients with Hepatitis B. Electronic medical records were reviewed to identify the subset of cases with congenital hepatitis B. Treatment-naïve liver biopsies were reviewed to assess patterns of liver injury. The inflammatory activity and fibrosis were scored using the Scheuer grading and staging system.

Results: Eight patients were identified (M:F= 1:1), aged 4 – 18 years at first biopsy. The mean interval between serologic diagnosis to first biopsy was 7.06 years (Range = 4–12 years). Histologic findings are summarized in Table 1. All eight biopsies showed no evidence of hepatocellular ground-glass inclusions. Pre-biopsy HBV DNA PCR was available on seven patients (Range:100,000 - >490,000,000 IU/mL; median :>170,000,000 IU/mL). One case demonstrated cirrhosis (Male, 12 years), while all remaining cases showed variable fibrosis, with no evidence of bridging fibrosis. Variable degrees of portal and lobular inflammation were detected in all cases. Two cases showed prominent sinusoidal lymphocytosis, mimicking that described in EBV virus hepatitis.

Table 1:

Histologic parameter			Number of cases (Total=8)	
Portal/periportalactivity (Scheuer system)		0	None	
		1	1	
		2	5	
		3	2	
		4	None	
Lobular activity (Scheuer system)		0	None	
		1	5	
		2	3	
		3	None	
		4	None	
Fibrosis (Modified Scheuer)		0	3	
		1	2	
		2	2	
		3	None	
		4	1	
Ground glass hepatocytes (Y/N)			None	
Nuclear features	None		3	
	Glycogenated/Optically clear nuclei		Zone 1	4
			Non-Zonal	1
Special features	Steatosis		2	
	Sinusoidal lymphocytosis		2	

Conclusion: Congenitally acquired chronic hepatitis B results in a non-specific chronic hepatitis pattern of liver injury. Characteristic ground-glass cytoplasmic inclusions were not seen within our series. Atypical patterns of inflammation such as sinusoidal lymphocytosis was seen in a subset of cases.

Platform III: Perinatal
Saturday, March 13
11:30am - 11:45am ET

14

Fetal Vascular Ectasia and Intramural Fibrin Deposition Do Not Add Meaningful Information to the Finding of Distal Vessel Fetal Vascular Malperfusion

J Stanek[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Background: Fetal vascular malperfusion (FVM), global or segmental, is one of the basic patterns of placental injury. This retrospective analysis was performed to study if histological changes in large vessels in addition to distal villous changes of FVM are associated with more abnormal fetal and placental phenotypes.

Methods: Frequencies of 26 clinical and 38 independent placental phenotypes of 202 successive placentas from ≥ 20 weeks pregnancy with distal vessel FVM without associated histological features of fetal vascular ectasia and/or intramural fibrin deposition (Group 1) were retrospectively statistically compared with 222 placentas with FVM coexisting with fetal vascular ectasia and/or intramural fibrin deposition histology (Group 2). FVM was diagnosed based on the Amsterdam criteria expanded by inclusion of the recently described lesions of segmental endothelial fragmentation by CD34 immunohistochemistry and segmental villous mineralization.

Results: Cases with FVM, fetal vascular ectasia and intramural fibrin deposition were slightly and statistically not significantly more common than the pure FVM seen in distal villi (52.4% vs. 47.6%, respectively). Group 2 placentas were heavier and associated with pregnancies with maternal smoking/substance abuse, polyhydramnios, and on histology, more frequent occluding and non-occluding thrombi and stem vessels obliteration, and less common choriodecidual hemosiderosis ($p<0.05$). There was no statistically significant differences in hypertensive conditions in pregnancy, diabetes mellitus, abnormal fetal heart tracing, perinatal mortality, fetal growth restriction, NICU stay, clinical cord compromise, and congenital malformations between Groups 1 and 2. Frequencies of anatomical cord abnormalities or abnormal cord attachment, acute and chronic placental hypoxic lesions, lesions of shallow placental implantation and high grade FVM did not statistically significantly differ between Groups 1 and 2 ($p>0.05$).

Conclusion: Fetal vascular ectasia and intramural fibrin deposition is not associated with additional risk for the fetus with placental distal vessel FVM, despite more common fetal vascular thrombi and stem vessel obliteration. Grading FVM may be more important than stressing on the presence of associated large vascular lesions.

Platform III: Perinatal
Saturday, March 13
11:45am - 12:00pm ET

15

Placental Chronic Histiocytic Intervillositis Correlates with Severity of Maternal Disease in SARS-CoV-2 Infection.

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Background: Chronic histiocytic intervillositis (CHIV) is a rare placental lesion that has recently been described as a risk factor for transplacental transmission of SARS-CoV-2. Our objectives were to identify a possible correlation between severity of maternal disease and the finding of CHIV in placentas from mothers with SARS-CoV-2 infection, and to determine the prevalence of CHIV in our population of COVID-19 positive mothers.

Methods: All placentas from COVID-19 positive mothers sent to the Pathology Departments of our healthcare system hospitals between April 8, 2020 and January 4, 2021, were examined grossly and microscopically. Retrospective review of the maternal and neonatal clinical histories, and correlation with placental histological findings were performed.

Results: CHIV was identified in three out of 18 placentas from COVID-19 positive mothers (3/18; 16%). Retrospective review of maternal clinical histories from these three mothers revealed severe disease in two of them, including abnormal liver function tests, low platelets and coagulopathy requiring intensive care. Both were third trimester pregnancies, and delivered liveborn infants by C-section. One infant was COVID-19 positive and one was COVID-19 negative. The third mother presented during the second trimester with fever, bleeding and intrauterine fetal demise, and delivered vaginally. The COVID-19 positive mothers without placental CHIV (15/18) were asymptomatic or showed mild symptoms. In this group, there were 15 liveborn infants and one stillbirth (twin). All the liveborn infants were COVID-19 negative.

Conclusion: In our series, the presence of placental CHIV was associated with severe maternal disease, but not necessarily with transplacental transmission of SARS-CoV-2. This observation would support host microbiological or immunological factors, such as viral load or presence of maternal cytokine storm, as possible explanations for the placental findings. Larger studies are necessary to fully understand the maternal and fetal response to COVID-19 infection occurring during pregnancy.

Platform III: Perinatal
Saturday, March 13
12:00pm - 12:15pm ET

16

Characterization of Vitelline Vessel Remnant (VVR) Circulation in the Umbilical Cord and Documentation that VVR-Derived Funisitis is a Sensitive and Specific Predictor of Histological Evidence of Smniotic Fluid Infection.

***J Wright*[1]**, *J De Guzman*[1], *C Horn*[1], *L de Koning*[1], *M Brundler*[1], *W Yu*[1]; [1]University of Calgary, Calgary

Background: Vitelline vessel remnants (VVRs) are poorly understood persistent embryonic vessels in umbilical cords that arise from the vitelline circulation, which normally regresses at about 10 weeks gestation. VVRs are found in the cords of approximately 4-11% of placentas processed in pathology laboratories. While these remnants retain an active circulation that can generate an inflammatory response (Wright JR Jr. Pediatr Develop Pathol. 2019; 22(4):279-287), the circulation within VVRs has never been studied and is poorly understood.

Methods: We prospectively identified VVR cases during routine placental microscopic examination, and identified two main histological patterns. In some instances, cord VVRs were catheterized with the aid of an operating microscope and injected with dilute ink. The progression of the injected ink was sequentially photographed, and sections were taken for histology in 5 cm intervals.

Results: Seventy VVRs were identified in a six-month period. Two main histological patterns were found: (1) paired thin-walled vessels (~90%) and (2) unpaired thin-walled vessels (<10%). Ink injections demonstrated that paired VVRs normally complete their circulation within the cord via capillary plexuses bridging between the vitelline artery and vein remnants; in some instances, the afferent and efferent vessels may also connect via a terminal “hairpin turn.” Unpaired VVRs (vitelline artery remnants) traverse the entire length of the cord and then anastomose with the primary placental circulation. Overall, we found neutrophilic inflammation arising from VVRs in 54.3% of the 70 cases, and coined the term “VVR-derived funisitis” for this entity, which was found to have a strong association with histological evidence of amniotic fluid infection elsewhere in the placenta. Its overall sensitivity and specificity were 0.94 and 0.88; when VVR-derived funisitis was severe or diagnosed in the third trimester, specificity rose to 1.0.

Conclusion: To the best of our knowledge, this is the first description of circulatory patterns in VVRs. VVR-derived funisitis was identified in examples of both paired and unpaired VVRs.

Platform III: Perinatal
Saturday, March 13
12:15pm - 12:30pm ET

17

CD34 Immunostain Increases the Sensitivity of Diagnosing Segmental Fetal Vascular Malperfusion in Stillbirth

A Drach[1], *J Stanek[1];* [1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Background: Fetal vascular malperfusion (FVM), after chorioamnionitis and maternal vascular malperfusion, is most helpful in histological evaluation of stillbirth, but most H&E lesions of segmental FVM appear only after several days after the inciting event, and postmortem regressive changes may obscure the pre-existing lesions of segmental FVM, but they are usually diffuse/global. We have previously found that the CD34 immunohistochemistry can reveal the incipient segmental FVM or on-going FVM with its temporal heterogeneity.

Methods: 25 independent clinical and 48 placental phenotypes were examined in 100 stillbirths at ≥20 week gestation. FVM was diagnosed in accordance with the Amsterdam criteria, expanded by our interpretation of the immunostain. 34 cases showed no FVM by H&E or immunohistochemistry (Group 1), 36 placentas showed segmental FVM by H&E (sclerotic villi, hypovascularity, stromal vascular karyorrhexis, mineralization) (Group 2), and 30 placentas showed no segmental FVM by H&E examination, but showed segmental endothelial fragmentation by the immunostain, or low grade FVM by H&E, subsequently upgraded to high grade by immunohistochemistry. Statistical significance ($p<0.05$) was calculated via chi-square analysis or analysis of variance.

Results: Poor or absent prenatal care and features of umbilical cord compromise were statistically significantly more common in Group 2. The CD34 immunostain revealed early /incipient FVM in 30% of stillbirth, which was not evident on H&E examination. Preuterine pattern of chronic hypoxic placental injury was most common in Group 1, erythroblastosis of fetal blood, chorionic disc microcysts, multinucleate trophoblasts in decidua basalis, fetal vascular ectasia, fetal vascular thrombi, and intramural fibrin deposition were most common in Group 2. Hypertrophic and hyaline necrosis/atherosis of spiral arteries were most frequent in Group 3. The remaining clinical and placental phenotypes, including the umbilical cord abnormalities, did not show statistically significant differences.

Conclusion: This analysis confirmed the leading role of placental examination in evaluation of stillbirth. With routine CD34 immunostaining, the FVM became the most common pattern of placental injury in stillbirth. Although Group 2 featured most common abnormal clinical and placental phenotypes, the adding the CD34 immunostain doubled the number of FVM cases by upgrading the low grade to high grade FVM or diagnosing the new incipient FVM (low grade or high grade) not seen on H&E stained slides. Because the high grade segmental FVM diagnosed by CD34 immunostain portends same poor outcome for the fetus as that diagnosed on H&E stained slides, the immunostain may be diagnostic or contributory in explaining the cause of otherwise unexplained stillbirth.

Perinatal Poster
Virtual Poster Viewing

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SARS-CoV-2 Placental Infection with Characteristic Histologic Features and Poor outcome

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Background: To date there are over 70 studies describing placentas from pregnant women diagnosed with COVID-19. The majority reported a wide range of nonspecific pathologic findings and many placentas from COVID positive mothers still show no significant pathology. The combination of histiocytic-neutrophilic intervillositis, trophoblast necrosis and increased perivillous fibrin deposition is recently recognized as frequent finding in SARS-CoV-2 infected placentas and appears to be associated with higher risk of intrauterine fetal transmission. We report three cases of COVID-19 positive pregnant women with poor outcome.

Methods: Case 1: Patient presented with decreased fetal movements at 31 weeks gestation. Cesarean section performed for non-reassuring fetal heart tones. Maternal history suggestive of prior COVID symptoms. PCR nasopharyngeal swab was negative and IgG was positive on admission. She delivered a viable infant who required neonatal intensive care.

Case 2: Patient presented at 23 weeks gestation with mild cold symptoms for 2 days followed by loss of taste and smell. She tested positive for covid-19. 4 days later she developed an episode of suprapubic pain and found to have an intrauterine fetal demise.

Case 3: Patient presented at 20 weeks gestation with vaginal bleeding and cramping. Ultrasound revealed an enlarging placental hematoma suspicious for abruption. Routine COVID-19 test on admission was positive. With further questioning, the patient reported that she had mild congestion and cough 2-3 weeks earlier. She was placed on aspirin early in this pregnancy for chronic hypertension and history of pre-eclampsia in 2 previous pregnancies. Vaginal bleeding stopped and 1 week later, she delivered a fetus and placenta at home.

Results: All three placentas showed histiocytic-neutrophilic intervillositis associated with trophoblast necrosis and increased perivillous fibrin deposition. In addition, large parenchymal hematoma was present in the placenta from patient 3. CoV-2 RNA in situ hybridization showed strong expression of viral RNA in sections of the placentas from patients 1 and 2 and it was negative in the third patient. The fetus of patient 2 showed no evidence of active infection but CoV-2 RNA in situ hybridization showed weak positivity in the intraalveolar and intestinal intraluminal contents likely reflecting infected amniotic fluid.

Conclusion: SARS-CoV-2 appears to rarely infect the placenta and there are increasing evidence for vertical intrauterine transmission. Placental and fetal examination can provide critical information to identify underlying causes of adverse pregnancy outcomes during the current pandemic. Viremia may occur in pregnant women who have mild symptoms or even asymptomatic.

Perinatal Poster
Virtual Poster Viewing

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Investigating Placental Pathologies in Pregnant Women with and Without SARS-CoV-2: A Systematic Review and Meta-analysis

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Background: There is a need to understand if SARS-CoV-2 has the capacity to contribute to diseases of the placenta. Placental pathology results are conflicting, with some evidence suggesting specific placental pathology findings induced by SARS-CoV-2. Patberg et al found that cases were more likely to display evidence of mural fibrin deposition [32.5% (25/77) vs. 3.6% (2/56)] and villitis of unknown etiology (VUE) [20.8% (16/77) vs. 7.1% (4/56)] in comparison to controls. In contrast, He et al reported no significant differences in individual or group gross or microscopic pathological features. A systematic review was conducted in light of the conflicting evidence.

Methods: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946- November 17, 2020) and Embase (1980- November 17, 2020) databases were searched. Case series, case-control and cohort studies of asymptomatic and symptomatic pregnant women, who tested positive for SARS-CoV-2 on admission, as validated by laboratory confirmed positive antibody testing or using real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) were included. Literature reviews, systematic reviews, editorials, conference abstracts, and commentaries were excluded. The primary endpoints were any placental pathology syndromes, as identified by the Amsterdam placental workshop group consensus.

Results: Six hundred and twenty-seven articles records were identified, resulting in 481 records for level I screening. After full-text screening (n=41), there were 12 eligible studies remaining for narrative synthesis. Eight (67%) were conducted in the United States. Five (42%) were case control studies, four (33%) case series, and three (25%) retrospective or prospective cohort studies. In total, 507 pregnant women with SARS-CoV-2 who had complete placental pathology reports were examined, in comparison to 18 035 controls. Documented placental pathologies from all studies included: chorioamnionitis (73/507,14%); fetal vascular malperfusion (54/507,11%); maternal vascular malperfusion (42/507, 8%); and chronic villitis and/or chronic deciduitis (124/507, 24%). In contrast, 43% (7791/18035) controls demonstrated any feature of maternal vascular malperfusion; 53% (9624/18035) fetal vascular malperfusion; and 37% chronic inflammatory pathology with both low-grade chronic villitis and chronic deciduitis with plasma cells (6739/18035).

Conclusion: Our findings demonstrate higher prevalence of placental pathologies in controls than cases; however, further investigation through a meta-analysis is warranted to determine if pregnant women with versus without SARS-CoV-2 are at a higher risk of having placental pathologies, while considering maternal comorbidities including hypertensive diseases, diabetes and obesity.

Perinatal Poster
Virtual Poster Viewing

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Histological Features of Shallow Placentation Are Associated with Abnormal Clinical and Placental Phenotypes

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Background: Histological features of shallow placental implantation (SPI) such as excessive amount of extravillous trophoblasts measured by increased number of cell islands and/or placental septa in the chorionic disc, chorionic microcysts of placental membranes and chorionic disc, decidual clusters of multinucleate trophoblasts, and placenta creta, were previously individually reported in association with various clinical and placental abnormalities. This retrospective statistical analysis of a large placental database statistically compares placentas with and without a composite group of features of SPI.

Methods: 24 independent abnormal clinical and 43 other than SPI placental phenotypes were compared between 4745 placentas without (Group 1) and 1468 placentas with one or more histological features of SPI (composite SPI group) (Group 2). Placentas were received for pathology examination at a discretion of obstetricians. Placental lesion terminology was consistent with the Amsterdam criteria, with addition of other lesions described more recently.

Results: Cases of Group 2 featured statistically significantly (p Bonferroni<0.001) more common than Group 1: gestational hypertension, preeclampsia, oligohydramnios, polyhydramnios, abnormal umbilical artery Dopplers, induction of labor, cesarean section, EXIT procedure, perinatal mortality, fetal growth restriction, congenital malformation, abnormal 3rd stage of labor, deep (decidual) meconium penetration, intravillous hemorrhage, villous infarction, membrane laminar necrosis, erythroblastosis of fetal blood, hypertrophic decidual arteriopathy, spiral artery hyaline necrosis/atherosis, uterine hypoxic injury, postuterine hypoxic injury, intervillous thrombus, segmental villous hypovascularity/avascularity, segmental villous mineralization, stem vessel obliteration, fetal vascular ectasia, intramural fibrin deposition, fetal vascular thrombus, hypercoiled umbilical cord, hypocoiled umbilical cord, stem perivascular edema, and other umbilical cord abnormalities. Acute chorioamnionitis was more common in Group 1 than in Group 2.

Conclusion: Histological features of SPI reflecting maldistribution/shallow myometrial invasion of extravillous trophoblasts are nonspecific but are associated with 45.8% of abnormal clinical (not only hypertensive condition of pregnancy) and other abnormal placental phenotypes (51.2%) such as acute and chronic hypoxic lesions, global and segmental fetal vascular malperfusion, umbilical cord abnormalities, and choriodecidual hemosiderosis, with only acute chorioamnionitis less common than in other placentas. Therefore, they should be regarded as an independent category of placental lesions.

Perinatal Poster
Virtual Poster Viewing

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Several Cases of Single Umbilical Artery Associated with Unusual Genetic, Familial, and Clinical Histories: Searching for Commonalities to Identify Underlying Candidate Genes

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Background: Single umbilical artery (SUA) is a condition in which there is one artery and one vein in an umbilical cord. It may be an isolated finding, may be seen associated with twinning, or in association with many congenital anomalies. It is known to be more common at the extremes of maternal age, in males, and in those of Eastern European descent. Several theories exist regarding the development of SUA, however the cause remains largely unknown. We seek to evaluate several unique cases in the context of genetic findings, family histories, and clinical histories to suggest genetic developmental pathways for further evaluation in an attempt to identify potentially influential candidate genes.

Methods: Pathology cases at Penn State Health Hershey Medical Center from 2019-2020 were prospectively reviewed for cases of single umbilical artery associated with unusual genetic findings, family histories, or clinical histories. These cases were evaluated with a goal of seeking similarities in underlying developmental pathology. Of those cases reviewed, three cases were selected that highlight possible similarities in underlying developmental pathology.

Results: In the first case, the mother of an infant with SUA had a clinical history of widespread metastatic melanoma from an early age and a variant gene in APC was identified. The second case involved a patient with Mosaic Monosomy X; of note in this case, the patient's mother had congenital albinism and nystagmus of uncertain etiology. The third case of single umbilical artery occurred in the cord of a term female infant that was found to have double-outlet right ventricle combined with a large sub-aortic ventricular septal defect as well as absent nasal bones, sandal gap toes bilaterally, and a very large/deep sacral dimple. The combined features of this case, and of these cases as a group, suggest neural crest genes as potential candidate genes.

Conclusion: An argument is made for the influence of neural crest genes (one gene can be active during different stages of development) in SUA. In an attempt to correlate the findings of these cases, neural crest candidate genes offer the best possible explanation for constellation of findings across multiple cases. The cause of single umbilical artery remains unknown, and a focus on identifying candidate genes is necessary. By analyzing such interesting cases together, WNT or SHH pathways, or other neural crest development pathways in general can be implicated in SUA. Specific genes involved in neural crest development pathways should be evaluated further in the context of perinatal development in relationship to the development of single umbilical artery.

Perinatal Poster
Virtual Poster Viewing

22

First Case of Placental Infection with Flavobacterium Oncorhynci Identified in a 28-week Stillborn

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Background: Placental examination for intrauterine death and recognition of fetal death due to placental infection are paramount to accurately determine overall epidemiology and pathogenesis of gestational infections.

Methods: We present a case of intrauterine fetal death in a 19-year-old mother from Nunavut, Canada, who delivered a macerated stillborn baby most consistent with 28 weeks-gestational-age. A complete autopsy was requested and performed, including examination of the fresh placenta.

Results: No lethal fetal anomalies were identified. Histologic examination of the placenta showed necrotizing inflammation with a prominent, nearly monomorphic, population of Gram-negative bacilli along the amniotic surface. Focal colonies of fungal elements were also present. Immunohistochemistry for Treponema pallidum was negative. 16sRNA gene sequencing analysis performed on formalin-fixed, paraffin embedded tissue at the National Microbiology Laboratory in Winnipeg identified Flavobacterium oncorhynchi.

Conclusion: Flavobacteria are found in soil and fresh water in a variety of environments. Several species are known to cause disease in freshwater fish. As per the authors' knowledge, this is the first case of F. oncorhynchi associated with human infection.

Perinatal Poster
Virtual Poster Viewing

23

Massive Perivillous Fibrin Deposition and Chronic Intervillositis: Potential Placental Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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Background: Massive perivillous fibrin deposition (MPFD) and chronic histiocytic intervillositis (CHI) are both very rare entities individually. Both are associated with poor fetal outcome and high risk of recurrence. Their co-occurrence has been described, but for most cases the cause remains unknown. Risk factors include autoimmune disorders, coagulopathies and viral infection. Here, we present a placenta with coexisting MPFD and CHI. Patient is a 31-year old G7P4 female who delivered a stillborn fetus at 33 weeks and 4 days gestational age. The pregnancy was unremarkable up until 32 weeks 3 days gestation when she developed fever and chills and PCR test confirmed positive for SARS-CoV-2. 8 days later, she presented with irregular contractions and decreased fetal movement. Ultrasound confirmed intrauterine fetal demise (IUFD). She underwent induction of labor and delivered a stillborn male fetus.

Methods: Autopsy and placental examination including H&E and CD68 immunohistochemical stains were performed.

Results: Autopsy revealed a mild to moderately macerated male fetus with growth and maturation appropriate for gestational age. No major congenital anomalies were identified. The autopsy findings were consistent with hypoxic stress changes including petechial and visceral acute hemorrhages, hepatic steatosis, moderate stress involution of the thymus and germinal matrix hemorrhage. The placental examination showed a small placenta for gestational age (290g) and MPFD involving 90-95% of the placental parenchyma in association with extensive histiocytic infiltration of the intervillous space as highlighted by CD68 staining. Placental insufficiency secondary to these pathologic findings is the most likely cause of IUFD.

Conclusion: MPVFD and CHI are rare and poorly understood placental lesions. In this case, the specific etiology is unknown, but the recent maternal infection with SARS-CoV-2 does raise the possibility of an infectious etiology. The occurrence of trans-placental transmission of the virus remains highly debated since the outbreak of coronavirus disease 2019 (COVID-19). While it is still difficult to present a comprehensive overview of the time course of SARS-CoV-2 infection and morphologic alterations of the placenta, several case reports and case cohorts analyzing the placental pathology have suggested potential placental pathologic features associated with SARS-CoV-2 infection including MPFV as well as CHI. There are increasing numbers of placentas from mothers positive for SARS-CoV-2 showing these placental injury patterns. This highlights that pathologists must be familiar with these entities and aware of potential adverse fetal outcomes during the current COVID-19 pandemic, especially considering that the majority of pregnant women appear to have mild symptoms.

Pediatric Poster
Virtual Poster Viewing

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Chronic Recurrent Multifocal Osteomyelitis (CRMO) a Study of 12 Cases From One Institution and Literature Review

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Background: Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a poorly defined, heterogeneous entity. It is a form of seronegative arthropathy that occurs predominantly within the pediatric population, with a waxing and waning clinical course over a period of many years. Pathologic examination is the gold standard for diagnosis that can also help to exclude infection, osteonecrosis, and malignancy. Many hypotheses about the underlying cause of CRMO have been recently proposed including immune dysregulation with imbalance between pro-inflammatory cytokines Interleukin-6 and Tumor Necrosis Factor (TNF). Rare cases occur in the same families suggesting a genetic component and we observed a relationship between CRMO and GALNT3 mutation in two siblings, but not the rest of our patients. The aim of the study is to characterize the pathological features and evaluate the latest theories on pathogenesis of the disease.

Methods: A retrospective review of patient charts including data on age, gender, clinical presentation, imaging studies, therapeutic approaches, and follow-up.

Results: Twelve patients (5 males and 7 females) were identified over a span of 7 years, age range of 1 to 16 years (mean of 8.3 years). Diagnosis of 8 patients was delayed since they were initially considered as having conventional osteomyelitis. However, the diagnosis of CRMO was reached after the appearance of second lesion, and due to lack of response to antibiotics. Imaging revealed the involvement of multiple bones. Biopsies showed bone necrosis with mild neutrophilic and monocytic infiltrate, with reactive changes and mild marrow fibrosis. All bacterial, fungal, and mycobacterial cultures were negative. Two patients were siblings, who tested positive for GALNT3 mutation. Patients were treated with anti-inflammatory medications and steroids, with 9 of these patients responded to therapeutic interventions, with complete healing. The other 3 had recurrent lesions, including at the same sites. The follow-up period was 6 months to 7 years

Conclusion: Bone biopsy is a powerful tool to diagnose this often elusive entity in correlation with imaging and culture findings. CRMO should be included in the differential diagnosis of bone lesions in children. It is now believed that this phenomenon may reflect a form of immune dysregulation with an imbalance of pro-inflammatory and anti-inflammatory mediators of interleukin family, with resulting increased RANKL expression and activation of osteoclasts. There is also a genetic component of the disease which is illustrated by FBLIM1 deficient mouse models as well as the GALNT3 mutation that we observed in two related patients.

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Core Biopsies for Chronic Recurrent Multifocal Osteomyelitis: 7 Year Retrospective Review with Radiologic and Microbiologic Correlation.

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Background: Chronic recurrent multifocal osteomyelitis (CRMO) is a debilitating disease characterized by inflammation in and around the bones. Children present with episodes of pain, joint swelling, skin erythema, and sometimes fever. CRMO can lead to abnormal bone growth, bone deformity, and fractures. Bone biopsies are performed to establish a diagnosis in many cases. Correlation of histologic changes with clinical findings, radiologic features and microbiology can be challenging.

Methods: Institutional records were queried for bone biopsies obtained from patients with a clinical suspicion of CRMO from January 2014 to December 2020. The clinical history, imaging features and microbiologic culture results of 31 cases of CRMO were reviewed with the histologic features of the bone biopsy.

Results: Thirty one patients were identified (M: 17, F: 14), aged 2 to 16 years at diagnosis. All 31 had elevated inflammatory markers and a clinical diagnosis of CRMO. All the cases had either X-ray, CT or MRI studies. The tibia was the most commonly involved site with other sites included metacarpals, iliac bones, femur, clavicle, and vertebrae. The imaging findings varied with most cases showing nonspecific edema, periosteal reaction and increased signal abnormalities. Only 3 cases showed evidence of bone necrosis or sclerosis.

All corresponding biopsies were adequate for evaluation. Histopathology varied, with 18 of 31 cases showing changes supportive of chronic osteomyelitis (marrow space fibrosis associated with plasma cell-dominant inflammation and necrotic bone). Ten cases showed scattered plasma cells and scarring. The remaining 3 cases showed variable edema, fibrosis, and reactive changes not diagnostic of CRMO. Two patients were subsequently diagnosed with acute lymphoblastic leukemia, and 2 others with Crohn disease. Six patients were on adalimumab and/or methotrexate for CRMO and were stable. None of the 31 patients had any growth on culture studies.

Conclusion: Core biopsy of bone is often done to confirm clinical suspicion for CRMO. However, there is a paucity of histologic findings, mostly nonspecific findings on imaging and cultures are seldom contributory. Histologic changes of scarring, patchy plasma cell infiltrates without devitalized bone, and focal chronic inflammation are most prevalent. Imaging shows edema, periosteal reaction, sclerosis, and multifocality. A well-defined subset of diagnostic histologic changes are lacking in CRMO. Larger studies are necessary to further categorize imaging and histology to develop diagnostic algorithms.

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Apoptosis in Gastric Mucosa is Not a Rare Finding in Patients Without a History of Bone Marrow Transplant

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Background: Pathologic examination of mucosal biopsies from the gastrointestinal tract plays a critical role in the diagnosis of graft-versus-host disease (GVHD). Gastric pit apoptosis is a histological hallmark of GVHD, and it is diagnostic of gastric GVHD with negative viral studies and a medication history that excludes mycophenolate mofetil (MMF), proton pump inhibitors (PPIs) or non-steroidal anti-inflammatory drugs (NSAIDs). Compared to the antrum mucosa, the gastric fundus is considered immune to the reported histologic changes induced by PPIs and does not display apoptotic bodies (AB). Herein, we report our observations on the presence of gastric ABs in the ambulatory setting and their clinical correlation in pediatric patients.

Methods: 28 consecutive gastric biopsies were prospectively identified in pathology practice. Clinical history was retrieved from electronic medical records. The following histologic parameters were recorded: AB number and frequency, other pathologic changes in the background mucosa and other parts of the upper gastrointestinal tract.

Results: Of the 28 gastric biopsies from 28 patients examined, 13 (46.4%) patients (age range 3.5 to 18.4 years, mean age 12.6 years; 7 females and 6 males) had ABs. A total of 16 biopsy pieces had ABs: these were located in both oxyntic and antral mucosa in 3 patients, limited to antral mucosa in 8 patients, only in the oxyntic mucosa in 1 patient, and the last patient had ABs in the oxyntic mucosa without concurrent antrum biopsy. Most biopsy pieces (11/16) had 1 AB, 3 had 2, and one antral mucosa had 3 ABs. The frequency of ABs varied from 12.5% (1/8) to 62.5% (5/8) in serial sections. The background mucosa showed no pathologic changes in 6, and chronic inactive gastritis in 7. Other pathology included fundic gland polyp (1) and pancreatic metaplasia (1). Six patients had concurrent terminal ileal biopsies, and crypt ABs were seen in 2, which also showed marked intraepithelial lymphocytosis. Four patients had a history of inflammatory bowel disease, and ileal crypt apoptosis was not seen when biopsied (2 patients). One patient reported no medication history. All other patients had taken multiple medications, including PPIs in 7 (duration one week to 18 months) and polyethylene glycol in 4 (duration 2 weeks to 18 months). Other medications included anti-depressants (2 patients), mesalamine (2 patients), histamine-2 blockers (2 patients), and NSAIDs (1 patient).

Conclusion: Gastric mucosa ABs are not a rare finding outside of bone marrow transplant recipients in pediatric patients. There might be coexisting ileal crypt apoptosis. Fundic mucosa is less likely to have ABs, but it is not immune to possible medication effects. Gastric mucosa pit apoptosis can be caused medications beyond MMF, PPIs and NSAIDS.

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Liver Explants of Biliary Atresia Patients Transplanted in Adulthood Show Features of Obliterative Portal Venopathy.

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Background: Background:Timely Kasai portoenterostomy (KP) in biliary atresia (BA) patients can restore bile flow; extending the age at liver transplantation (LT) to adolescence/adulthood. This study is a follow-up to a recent pediatric study that showed features of obliterative portal venopathy (OPV) in explants of BA patients with a successful KP.

Methods: Methods: Adult liver explants of BA patients (2014-2016) were studied along with clinical, laboratory and imaging records.

Results: Results: Three explants were identified, all females, with age at LT 25, 32, and 33 years respectively. All 3 were diagnosed at birth, with age at KP ranging from 8 days to 16 weeks. Conjugated bilirubin had normalized within 6 months of KP and the post KP course was complicated by portal hypertension (PHTN) with or without recurrent acute cholangitis (RAC). Cholestasis was severe in pt #1 (9 yrs of RAC), moderate in pt #2 (3 yrs of RAC) and absent/minimal in pt #3 (no RAC). All 3 explants showed portal sclerosis with loss of portal venules, bile duct attenuation and mild medial hypertrophy of hepatic artery branches. Variable fibrointimal thickening and occlusion of large hilar and extrahepatic portal vein were seen in all 3. Fibrosis was diffuse and advanced in pt #1 and minimal peripheral in pt #3.

								Explant Pathology		
No	**Age at LT (yrs)**	**Age at KP**	**PHTN in 3 years of KP?**	**Cirrhosis on US with reversal of portal flow**	**Age at onset of RAC**	**Indication for LT**	**c-bil at LT (mg/dl)**	**Cholestasis**	**HPS**	**Fibrosis stage**
1	25	8 days	Yes, sclerotherapy	Yes	16	RAC (9 years) and PHTN with sudden decompensation	32	Severe	Yes	03/04/04
2	32	16 weeks	Yes, banding	Yes	29	RAC (3 years) with PHTN	19.2	Moderate	Yes	02/03/04
3	33	8 weeks	Yes, TIPSS	Yes	N/A	PHTN, no RAC	2.8	None/minimal	Yes	Incomplete septal, peripheral only

c-bil: Conjugated bilirubin; HPS: Hepatoportal sclerosis; RAC: Recurrent acute cholangitis; TIPSS: Transjugular intrahepatic portosystemic shunt; USG: Ultrasound examination.

Conclusion: Conclusion: Adult BA explants show findings similar to pediatric patients with a successful KP. Cholestasis and biliary type fibrosis are related to episodes/duration of

RAC; that may or may not be present in every patient. PHTN is always present. Variable hilar/extrahepatic portal vein occlusion is prevalent likely leading to portal sclerosis and non-uniform delicate septal fibrosis with peripheral accentuation. In the context of optimal bile drainage, portal hypertension may not be due to biliary cirrhosis but possibly due to OPV. Vascular abnormalities of the PV system should be investigated in BA patients.

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Fatal Pediatric Streptococcal Infection: A Clinico - Pathological Study

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Background: Invasive Streptococcal infections (SI) in children commonly manifest as bacteremia, pneumonia, or meningitis resulting in significant morbidity and rarely fatality. There is a paucity of literature addressing the clinico-pathological features of fatal invasive SI in post-neonatal infants and children. We, therefore, undertook a review of autopsied patients where SI was the primary cause of death.

Methods: Our autopsy database was searched from January 1997 to December 2019 for pediatric deaths over the age of 28 days, in which a full post mortem examination was performed and the cause of death was SI. Pre-mortem clinical data including demographics, presentation and co-morbidities were extracted. Post-mortem findings of cases in which there was no predisposing factor for SI were further analyzed for sites of infection and species of Streptococcus species (Ssp). These clinical and pathological features of SI due to S. pneumoniae (SPn), S. pyogenes (SPy) and S. other (SO) (S. Agalactiae, S. Anginosis, S. Viridans) were compared.

Results: The cause of death was attributed to SI in 62 patients. 24 had medical conditions predisposing to infection. 4 had malformations or syndromes with no contributory role to SI and 34 were previously healthy. In the latter groups, Ssp was distributed as follows: SPn:17, SPy:14 and SO:7. Post mortem blood culture (PMBC) was positive (pure or mixed growth) in 54.3% of sepsis cases. Lung and CSF samples were positive for infection in 84.6% and 40%, respectively. Ages ranged from 5weeks to 16 years with a mean age of 3.96 years. 68.4% of deaths occurred above age of 2 years, 18.4% under 12 months and 13.2% between 13 to 24 months. The male to female ratio was 1.11:1. 13.2% were found unresponsive at home, 76.3% had sudden collapse or deteriorated rapidly and 10.5% died in hospital after at least 1day of admission. 76.3% were preceded by at least 1day history of prodromal symptoms (SPn:14/17, SPy:10/14, SO:5/7) and 34.2% of decedents had had sought medical attention prior to terminal presentation. Sudden collapse or rapid deterioration was frequent in both SPn and Spy groups (SPn:15/17, SPy:11/14, SO:3/7). There was a positive PMBC without a histologically confirmed organ site of infection e.g. pneumonia in 8 cases. Whereas, in 8 cases there was evidence of organ infection but the PMBC was negative.

Conclusion: Streptococcal infections especially SPn and SPy remain an important cause of sudden death in an otherwise healthy infant and child. Acute onset with rapid deterioration to death is a common clinical presentation highlighting the importance of preventive medical strategies. PMBC positivity in the absence of pathological evidence of infection confirms the importance of post mortem microbiological studies in pediatric autopsies.

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Intimal Hyperplasia of the Mesenteric Veins Mimicking Pediatric IBD: Case Report and Literature Review

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Background: Inflammatory bowel disease (IBD) is a diagnostic challenge. There is considerable overlap in clinical and radiologic findings with entities that are typically in the differential; including infections, medications and ischemia. The later is rarely suspected in the context of pediatric patients. Idiopathic myointimal hyperplasia of the mesenteric veins (IMHMV) resembles IBD, and is a defined cause of chronic colonic ischemia in adult patients. We report a pediatric case of intimal hyperplasia of the colonic mesenteric veins, initially diagnosed and treated as IBD.

Methods: This 13-year-old girl with trisomy 21 and neonatal history of duodenal atresia, had 1 week history of diarrhea, vomiting, abdominal pain and elevated inflammatory markers. CT scan demonstrated colonic and ileal mural thickening with terminal ileitis. Endoscopic biopsies were performed.

Results: 1st endoscopy; left colon unremarkable. Transverse and proximal colon showed discrete ulcers, erythema and pseudopolyps. Microscopy; lamina propria (LP) was edematous with minimal inflammation and prominent LP capillaries. She continued to have intermittent episodes of elevated inflammatory markers and bloody diarrhea. Repeat endoscopy was performed after 5 months. 2nd endoscopy; left colon with continuous erythema and discrete ulcers. Microscopy; similar findings as before, not typical for IBD. MR enterography; features of IBD with intense activity. Based on clinically suspected Crohn`s disease, oral prednisone was initiated. She later underwent exploratory laparotomy for sepsis and bowel obstruction. A full-thickness biopsy of the left colon showed similar but exaggerated LP capillaries. Submucosa demonstrated marked intimal hyperplasia of medium-sized veins and numerous dilated and hyalinized "arterialized" small vessels. The arteries were spared. The possibility of an underlying veno-occlusive abnormality (e.g. mesenteric) was raised, mainly IMHMV or similar lesions. MR angiography showed marked hypoperfusion of the colon. Non-visualization of the entire inferior mesenteric vein and attenuation of the lower segment of superior mesenteric vein. Clinical diagnosis of chronic colonic ischemia likely secondary to IMHMV was designated. The patient continues to do well with stoma and on normal diet with no therapies, 18 months later.

Conclusion: IMHMV is a rare entity and can be mistaken for IBD. Most affected patients are adults. Our case of a teenager signifies the importance of exclusion of ischemic causes regardless of age, especially when histopathology is atypical. Suggestive features on microscopy must be taken into consideration, for vascular imaging and avoidance of unnecessary treatment. In most cases, ileostomy and surgical resection is curative. If untreated, complications may be life threatening.

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GAB1-ABL1 Fusions in Tumors with Histologic Overlap with Infantile Fibrosarcoma/ "NTRK-Rearranged Spindle Cell Tumors"

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Background: Recurrent gene alterations in receptor tyrosine and/or cytoplasmic kinases have been described in infantile fibrosarcoma (IFS) and the provisional diagnostic category, "NTRK-rearranged spindle cell tumors." These tumors have unique clinicopathologic features including a spectrum of morphologies and variable CD34 and/or S100 expression. To date, these tumors have been reported to harbor a variety of activating alterations within the MAPK signaling pathway, including receptor tyrosine kinase (RTK) fusions (*NTRK1/2/3*, *RET*, and *MET)* or cytoplasmic kinase fusions or other activating alterations (*RAF1* and *BRAF)*).

Herein we present the first two cases of *GAB1-ABL1* fusions within the spectrum of IFS/"*NTRK*-rearranged spindle cell tumors," one of which showed therapeutic response to imatinib.

Methods: For both cases, clinicopathologic features were assessed, including patient demographics and outcomes, radiographic features, morphology, and immunophenotype. Next generation sequencing was performed on clinically validated platforms.

Results: Case 1: The patient is a 9-year-old female who presented with a 3.8 cm deep right axillary mass. Resection showed ovoid to spindle cells arranged haphazardly, separated by collagen bands. Other areas of the tumor showed storiform, herringbone, and fascicular arrangement of tumor cells. Variable hemangiopericytoma-like vessels were present. By immunohistochemistry, CD34 was variably positive; S100 and other markers were negative. This case was reported as a "solitary fibrous tumor" with a novel t(4;19)(q31.1;q34) translocation in 2004 (Pediatr Dev Pathol. 2004 Nov-Dec;7(6):653-60).

Case 2: The patient is 76-year-old female who presented with an 11.3 cm mass of the right anterior hip with invasion of right iliac bone. Needle core biopsy demonstrated monotonous, bland, ovoid to spindle cells haphazardly arranged in a background of densely collagenized stroma; prominent hyalinized vessels were present. By immunohistochemistry, CD34 was diffusely positive and S100 showed patchy positivity; panTRK showed weak cytoplasmic staining and all other markers were negative.

Next generation sequencing of both cases demonstrated GAB1-ABL1 gene fusions, corresponding to t(4;19) translocation described in case 1. Case 2 was treated with imatinib with 10% reduction in tumor size and decrease in enhancement on MRI; therapy was discontinued due to toxicity.

Conclusion: We present the first two cases of *GAB1-ABL1* gene fusions within the spectrum of IFS/ "*NTRK*-rearranged spindle cell tumors," and note that both cases had variable CD34 and/or S100 expression. Importantly, identification of this fusion offers the opportunity for targeted therapy with imatinib.

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Reoperation for Hirschsprung Disease: Two cases of Vanishing Ganglion cells

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Background: Hirschsprung disease (HD) is a genetic disorder characterized by circumferential aganglionosis of the rectum with variable proximal bowel involvement. This is due to failure of caudal migration of neural crest cells during embryogenesis, which causes functional bowel obstruction. Definitive therapy is surgical resection. However, some patients become symptomatic after initial surgery, are refractory to conservative medical management, and require another operative procedure. In most cases, this can be explained by pathologic findings. One important etiologic factor is the rare but distinct entity described as the ganglion cell "die back" phenomenon. In this phenomenon patients had normal ganglion cells present at the proximal resection margin during primary resection and develop recurrent symptoms. Upon reoperation, the ganglion cells seemingly vanish and are no longer present at the previously functioning and ganglionated site. Here we present two cases of HD patients who required reoperation to further characterize and investigate this poorly understood pathology.

Methods: A retrospective review of patient charts including data on age, gender, clinical presentation, imaging studies, therapeutic approaches, and follow-up.

Results: Both patients were full term male infants born without complication who presented with delayed passage of stool. Age at presentation was 5 and 12 days of life. Cystic Fibrosis was excluded, barium enema showed stenotic areas at the splenic flexure in patient 1 and the distal sigmoid colon in patient 2. Both patients underwent Soave transanal endorectal pull-through with the proximal margins of resection showing abundant circumferential ganglion cells for a length of 6 cm. Following pull-through, they experienced an asymptomatic period of normal bowel function ranging from 5-9 months post surgery. They underwent redo Soave pull-through which showed recurrent aganglionosis and hypertrophic nerves in the distal 5 and 6 cm. Patient 1 had no significant inflammation while patient 2 had a prominent eosinophilic infiltrate in the myenteric plexus. Both patients are asymptomatic with normal stooling two and six years post reoperation respectively.

Conclusion: "Die back" phenomenon of ganglion cells in HD is an acquired aganglionosis developing after the time of the primary pull-through. It is an important cause of reoperation in children and has yet to be fully elucidated. An autoimmune component may contribute as patient 2 had a brisk neurotropic eosinophilic infiltrate. However, this was not observed in patient 1. Other possible etiologies include post-operative ischemia/hypoxia, visceral neuropathy or signaling abnormalities within the residual ganglion cells themselves.

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Patient and Family Interactions are Infrequent but Generally Positive Experiences in the Practice of Pediatric Pathology

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Background: Recent studies have demonstrated patient interest in direct pathology consultation, with pilot programs showing positive results. Our aim was to examine the experiences and attitudes of pediatric pathologists toward seeing patients, with the goal of identifying areas to inform future practice.

Methods: A survey was distributed to pediatric pathologists at 10 institutions via RedCap. Questions covered frequency, reasons for, and impressions of prior patient interactions, and attitude toward seeing patients in the future. The option was provided to discuss experiences in an interview.

Results: Our 20 respondents included predominantly female pediatric pathologists (70%) with over 10 years of experience practicing pediatric pathology (70%) who sign out at least 75% pediatric pathology (65%). The majority reported seeing patients infrequently (once a year or less, 75%), while a few regularly see patients (multiple times per year, 25%). The most common reason was desire to understand the disease (70%), while aiding in decision making (35%) and patient empowerment (35%) were the next most common. Almost all described their experiences as very positive or positive (89%) and are at least somewhat interested in more regular patient interactions in the future (80%). A range of benefits and drawbacks were identified (Table 1). Interviews yielded instructive vignettes revealing both pitfalls and opportunities in patient/family interactions.

Table 1: Reported benefits and drawbacks of seeing patients

	Positives (# respondents)	Negatives (# respondents)
For patient care	Enhance understanding of diagnosis (14)	Risk of conflicting with care team (5)
	Provide reassurance (4)	Difficult to explain pathology to non-experts (5)
	Enhance trust, transparency (2)	Pressure from the family to do things not clinically indicated (2)
	Opportunity to express gratitude (1)	Hard to establish rapport in short time (2)
	Support research (1)	Seeing gross photos could be shocking (1)
		Pathologists not skilled at interacting with patients (1)
For the pathologist/field of pathology	Enhance understanding of the role of pathology (7)	Time consuming, no reimbursement (6)
	Improve job satisfaction, burnout (6)	Legal concerns (4)
	Clinical-pathologic correlation, enhance understanding of disease impact (6)	Emotionally draining (4)
	Encourage collaboration, improve rapport (5)	
	Inspire young patients to pursue pathology (1)	

Conclusion: Most pediatric pathologists report infrequent but positive patient interactions and a desire to see more patients in the future. Collated vignettes from a range of scenarios may provide information to help inform the structure of pathologist-patient interactions.

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Pediatric and Adolescent Gynecologic Pathology - an 11-Year Audit of Gynecological Surgical Procedures and Diagnoses in the Pediatric Age Group at the Health Science Centers, Manitoba, Canada.

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Background: The gynecological conditions in children and adolescents are gaining increased recognition, in spite of the fact they are not very common. The gynecologic pathology indicating surgical management in the pediatric and adolescent population is diverse and involves both internal and external genitalia. As these procedures typically do not account for a large proportion of the surgery burden at any single institution, limited, if any, literature characterizes the volume of procedures or the continuum of surgical gynecologic pathology in the pediatric population.

Methods: We undertook an 11-year retrospective study to determine the frequency and variety of gynecologic surgical procedures and pathological diagnoses in the Manitoba's pediatric population. We reviewed all gynecologic-surgical specimens submitted to Health Science Centre, followed by the patients' charts review. The pathology data base was inquired for all anatomic gynecology words including “cervix, fallopian tube, ovary, uterus, cervix, vagina, vulva, labia, hymen” in the Laboratory Information System. Electronic surgical pathology reports were reviewed to extract demographic, surgical, preliminary clinical and final pathological data. Data was tabulated, and given a numeric combination. The final numeric data was analyzed using STATA software (StataCorp, Version 15.1, College Station, TX, USA).

Results: We excluded all cytology specimens (18,483), products of conception (3,553), non-gynecologic specimens (48), autopsy (16), consults (92), cervix biopsies (718) related to screening cytology, duplicated or multiple specimen cases, or cases (17) not truly meeting the study criteria, i.e. gender assigning surgeries. This resulted in 369 patients with a mean age of 14.9±3.2 (range 0-18) years. Of these, 90.2% of patients were from Manitoba and 8.4% were from out of province. Procedures addressed pathology in both internal and external genitalia, and most commonly (45.4%) involved the adnexa, ovaries respectively. Most common diagnoses were related to non-neoplastic and benign neoplastic ovarian pathology, with only 13 malignancies (12 ovarian in origin; 1 synovial sarcoma of the vulva) identified in the studied interval.

Conclusion: Pediatric surgical gynecology represents a niche but diverse area of practice. In Manitoba, the majority of these procedures were performed by gynecologists at the only two tertiary care centers in the province. This study represents a broad overview of the frequencies and variety of gynecologic surgical procedures and pathological specimens of girls in Manitoba. Future research efforts should explore the subtleties of each anatomic site in terms of pathology, procedures, and patient outcomes.

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L-Cell Neuroendocrine Tumors Arising in Pediatric Crohn's Disease: A Report of Two Cases and Literature Review

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Background: Inflammatory bowel disease (IBD) is common in pediatric age group and carries an overall higher risk of gastrointestinal (GI) tumours, mostly adenocarcinoma. While well-differentiated neuroendocrine tumours (WD-NETs) of the luminal GI tract are rare with a heterogenous etiological association. A debatable risk for NETs in IBD has been proposed, linking luminal inflammation causing hyperstimulation of enteroendocrine cells, thereby leading to hyperplasia and neoplasia. This hypothesis remains to be proven. Nevertheless, NETs in the setting of IBD are not well characterized. We describe two pediatric patients with Crohn's disease with WD-NET of the rectum and appendix, respectively. Both tumours were phenotypically L-cell origin.

Methods: Case 1: 17-year-old male with refractory Crohn's disease and subsequent ileocolic resection. A rectal polyp arising in an uninflamed mucosa was identified on follow up colonoscopy. Case 2: 16-year-old male who underwent ileocolic resection for Crohn's disease. An incidental appendiceal wall tumour was found on histological assessment of the resected specimen.

Results: The histology and the immunoprofile were similar for both tumors (both were less than 1 cm). These tumors were characterized by monomorphic cells arranged in organoid nests, containing abundant eosinophilic granular cytoplasm and round nuclei with evenly dispersed fine chromatin. The Ki-67 index was less than 1%. No lymphovascular invasion was seen. The tumor cells were positive for cytokeratin 8/18, synaptophysin, chromogranin (weak, focal), glucagon and prostatic specific acid phosphatase (PSAP), by immunohistochemistry. Serotonin was negative. These were reported as grade 1 well-differentiated NET; L-cell type. No neuroendocrine cell hyperplasia, micro-nests or -foci were present.

Conclusion: Rectal and appendiceal NETs have two common phenotypic categories: enterochromaffin cell (EC) and L-cell. The L-cell NETs are pancreatic polypeptide, proglucagon-derived peptides and PSAP producing. In contrast to EC type, these do not secrete serotonin. We describe two cases of L-cell type WD-NET in pediatric patients with Crohn's disease. The immunophenotype of NETs in IBD is not well characterized. A recent study suggested that NE-cell proliferation and NETs in IBD may derive from L-cell type. However, the immunophenotype of NETs in IBD is not well characterized. Furthermore, although controversial, the L-cell NETs are reported to impart a more favourable prognosis than other types. Additional reports and prospective/retrospective studies detailing the cell of origin for NETs arising in the context of IBD, are warranted and will provide additional valuable insight into their pathogenesis and prognosis.

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Diaphragmatic Weight Correlates with Clinical Conditions and Mechanical Ventilation

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Background: Although the diaphragm accounts for up to 80% of the inspiratory phase, only a few studies have been devoted to its morphology and pathology. Recent attention has been drawn to its altered function in various conditions including disuse following prolonged mechanical ventilation. This study analyzes diaphragmatic weight (DW) in infants with various clinical conditions to determine which have affected DW.

Methods: During 1980 – 2020, 122 diaphragms were removed at autopsy in a consistent manner including exclusion of fibroadipose tissue. The DWs were correlated with clinical and autoptic data including sex, gestational age (GA), post conceptual age, birth weight (BW), ventilation status/ length of time on ventilation (LOTV), infant weight at autopsy (AW) and clinical diagnoses. The latter were 1) neuromuscular disease (NMD), 2) congenital heart disease (CHD), 3) multiple congenital anomalies (MCA), 4) congenital diaphragmatic hernia (CDH), 5) persistent pulmonary hypertension of the newborn (PPHN), 6) Miscellaneous, and 7) Controls (infants who died rapidly from causes not suspected to influence DW significantly). Multivariable linear regression analysis was performed to determine which variables were significantly associated with DW.

Results: 122 diaphragms were analyzed from infants and young children (M = 64, F = 58) 22 to 114 weeks post conceptual age. of which were male and 58 were female. GA ranged from 22 to 43 weeks. AW ranged from 340 to 4040 grams. 88 patients had assisted ventilation, and LOTV ranged from 1 to 2688 hours. DW was most strongly associated with AW ($r=0.70$, $P<0.001$). When adjusting for AW, both BW and GA showed a positive correlation with DW ($P<0.001$ and $P<0.001$). Of the clinical subgroups, MCA showed the lowest mean DW (14.8 grams), and PPHN showed the highest mean (28.4 grams). The average DW for the other clinical groups were Miscellaneous:17.9 grams; CDH: 20 grams; Controls: 20.1 grams; CHD: 20.8 grams; and NMD: 24.8 grams. LOTV was negatively correlated with DW (adjusted coefficient -0.005, $p=0.013$).

Conclusion: The factors influencing diaphragmatic weight are likely multifactorial. Body weight showed the greatest correlation with diaphragmatic weight indicating that body weight is an important variable when establishing normal reference vales for DW. The clinical groups with the lower mean DW included MCA, Miscellaneous, and CDH. The groups with the highest mean DW included PPHN and Controls. LOTV demonstrated a negative correlation with DW supporting reports describing decreased diaphragmatic thickness following prolonged assisted ventilation. Our study indicates the diaphragm is potentially an under-utilized portion of the autopsy and may provide additional support to contributory mechanisms of respiratory failure.

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Not Just Small Adults: A Case Report of Poorly Differentiated Thyroid Carcinoma in a Teenager Demonstrating Different Molecular Alterations Compared to Adult Populations

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Background: Poorly differentiated thyroid carcinoma (PDTC) is a follicular cell tumor with limited histologic evidence of follicular cell differentiation and intermediate characteristics between well differentiated and anaplastic carcinomas of the thyroid. PDTC accounts for less than 2% of thyroid carcinoma cases in the United States, and typically is seen in middle aged adults. Rare cases are seen in the pediatric and adolescent population.

Methods: A previously healthy 15-year-old male presented to the Otolaryngology division with a neck mass that had been present for 1 year. Physical exam revealed an enlarged thyroid gland, with no palpable lymphadenopathy. Ultrasound showed an enlarged thyroid with homogenous echogenicity. No calcification was noted. A fine needle aspiration performed at an outside hospital revealed a Bethesda Category V lesion (suspicious for malignancy) with a comment raising the possibility of medullary carcinoma. Subsequent tests demonstrated hypothyroidism (high TSH, low free T4), negative serum calcitonin, negative PTH, and negative CEA. A total thyroidectomy was performed.

Results: Grossly, the specimen had a white-tan to pink-tan heterogeneous cut surface. Microscopically, tumor cells formed nests (insulae) separated by sclerotic septae, trabeculae, and solid sheets with increased mitotic activity and coagulative necrosis. No well-defined nuclear features of papillary thyroid carcinoma were seen. Scattered small follicles containing colloid were seen throughout. Immunostains were positive for cytokeratins AE1/AE3, Thyroglobulin, TTF-1, and PAX-8 in these tumor cells. In select areas, sheets of tumor cells had a cribriform architecture, prominent molding, increased mitotic activity with atypical mitoses, and anaplastic appearing nuclei. Extensive lymph-vascular invasion was present. The tumor cells with the cribriform pattern were negative for thyroglobulin, and positive for the other listed markers. Both the insular and cribriform patterned tumor cells were negative for calcitonin, synaptophysin, and chromogranin. A diagnosis of PDTC was rendered. Pediatric Oncomine was performed and revealed mutations in DICER 1 (c.5437G>A p.Glu1813Lys) with an allele frequency of 84% and TP53 (c.586C>T p.Arg196) with an allele frequency of 88%.

Conclusion: This case emphasizes that the molecular alterations in pediatric PDTC differ from those seen in adults. Accordingly, PTDC in children should be considered as a distinct entity. More awareness is needed for this rare tumor among pathologists, particularly in tertiary institutions, where it is more likely to be encountered.

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Constitutional Mosaicism for Ring Chromosome 22 and Monosomy 22 in a Patient with Atypical Teratoid/Rhabdoid Tumor and Clinical Diagnosis of Fetal Alcohol Syndrome

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Background: Atypical teratoid/rhabdoid tumor (ATRT) is an uncommon brain malignancy of infants and young children associated with biallelic alterations in the SMARCB1 tumor suppressor gene at chromosome 22q11.23. Rare case reports describe an association between ATRT and constitutional structural chromosomal abnormalities such as ring chromosome 22 (abbreviated as r(22)) and 22q13.3 deletion (Phelan-McDermid Syndrome). The clinical manifestations of these chromosomal abnormalities in infancy, including developmental delay and mild facial dysmorphism, may be difficult to distinguish from other etiologies such as fetal alcohol syndrome (FAS). We present a case of constitutional mosaicism for r(22) and monosomy 22 identified at autopsy in a 3 year old female with pineal region ATRT, developmental delay, growth failure, and clinical diagnosis of FAS.

Methods: Antemortem neuropathologic evaluation and cytogenetic analysis was performed on the pineal region tumor. The patient died three weeks after tumor resection without chemotherapy, followed by complete autopsy with cytogenetic analysis of non-tumor tissue.

Results: Biopsy of the pineal region tumor demonstrated histologic features consistent with ATRT, including immunohistochemical loss of INI-1. The initial diagnosis was complicated by unusual foci of chondroid differentiation and mild serum/CSF AFP elevation. Antemortem karyotype of the tumor revealed loss of chromosome 22 in a subset of cells (45,XX,-22[14]/46,XX[6]). Autopsy revealed short stature (<2nd percentile), a sacral dimple, and possible facial dysmorphism, including a mildly flattened philtrum. Neuropathologic evaluation showed residual ATRT adjacent to the resection cavity and nearby ischemic infarcts; features of teratoma or residual chondroid foci were absent. Unexpected findings included a bicornuate uterus and streak ovaries, prompting constitutional cytogenetic evaluation (performed on grossly normal left kidney) revealing compound mosaicism for r(22) and monosomy 22 (mos 46,XX,r(22)(p11.2q13)[13]/45,XX,-22[7]). Other findings included decreased organ weights overall, acute bronchopneumonia, and mild hepatic sinusoidal congestion.

Conclusion: We describe ATRT with unusual foci of chondroid differentiation in a young child with clinical diagnosis of FAS, developmental delay, and growth failure. Constitutional compound mosaicism for r(22) and monosomy 22 was discovered at autopsy, possibly secondary to ring chromosome instability during mitosis. Autopsy also revealed a bicornuate uterus and streak ovaries, not previously reported in constitutional r(22). In young children with ATRT and developmental delay, constitutional chromosome 22 abnormalities should be considered. Such chromosomal abnormalities may also be a consideration in infants with suspected FAS.

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Second Malignant Neoplasm Twenty-Eight Years After Recovery of Congenital Cervical Neuroblastoma: Case Report and Review of the Literature

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Background: Second malignant neoplasms (SMN) in patients who have recovered from any childhood malignancy are seen in 4-15 percent of survivors. It is the second leading cause of death for survivors of childhood cancer, and this increased risk, particularly for the treated high risk neuroblastoma (NB) is related to the intensive multi modality therapies used for treatment. Most commonly in these patients, cited second malignancies are hematogenous, however solid tumors may occur in thyroid, breast and kidneys.

Methods: We present a case of an individual who developed colorectal adenocarcinoma of the sigmoid colon, twenty eight years after completion of his initial high risk NB therapy. A 29 year old male came to medical attention due to left lower quadrant abdominal pain, nausea and fulness for three 3 months which prevented him from completing simple tasks. He noticed eleven pound weight loss over two 2 months. Computed topography scan demonstrated a 6.4 cm mass in the proximal sigmoid colon, with associated adenopathy and a small pleural nodule. He was consequently referred for a colonoscopy. The patient is a cancer survivor, as he was diagnosed with congenital neuroblastoma (stage IV), diagnosed at two months of age following biopsy of a left sided cervical mass. He was a high risk patient (as defined by stage 4 disease, unfavorable histology and N myc amplification) at diagnosis.

Results: Endoscopic visualization of the proximal sigmoid colon identified a 20 cm large ulcerated mass. The histological examination revealed an invasive moderately differentiated adenocarcinoma. MMR immunohistochemistry revealed loss of MSH6, with preserved MLH1, MSH2, PMS2 nuclear positivity in the tumor cells. As an infant, he underwent treatment with radiation to the cervical spine and chemotherapy involving a total of 8100 mg/m 2 of cyclophosphamide, 205 mg/m 2 of doxorubicin, 510 mg/m 2 of cisplatin and 800 mg/m 2 of etoposide.

Conclusion: GI SMNs as a result of chemotherapy in this population are rare. The cumulative incidence of SMNs at 10 years is 1.8 percent and the cumulative risk of colorectal cancer at 30 years after primary malignancy is 0.1 to 22.4 per cent. Within the context of primary NB, the risk of a gastrointestinal SMNs of any type, in the absence of radiation exposure, with a cumulative incidence at 25 years, is 0.1 per cent. An association between high dose procarbazine and cisplatinum and GI SMNs has been characterized, however these patients had been irradiated. The MMR gene abnormalities identified in this patient is pending genetic testing. As per our knowledge, an association between Neuroblastoma and Lynch Syndrome has not yet been described in the literature.

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Primary Adrenal Malignant Rhabdoid Tumor in a 14-Year-Old Female

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Background: Malignant rhabdoid tumor (MRT) is a rare, aggressive tumor, occurring predominantly in children less than 3 years of age. Primary adrenal MRT is extremely rare, with less than 5 cases reported in the literature.

Methods: Clinical information and radiological data were retrieved from the electronic medical record. Routine and immunohistochemical stains, next generation sequencing (NGS) and chromosomal microarray analysis (CMA) were performed.

Results: A previously healthy 14-year-old female presented with left upper quadrant/epigastric abdominal pain. Imaging studies revealed an 8.0 x 8.0 x 6.5 cm, heterogeneous, partially enhancing mass along the superior margin of the left kidney encasing the adrenal gland, but not invading the kidney, spleen or colon. Surgical resection of tumor was performed. Grossly, the tumor was very friable. Microscopically, a hypercellular heterogenous neoplasm arising from the adrenal gland was identified. The tumor was composed predominantly of nests of densely packed primitive small round blue cells with focal true rosettes and areas of vague glandular epithelial differentiation and chondroid differentiation. Classic rhabdoid-type cytoplasmic inclusions were focally present. Mitoses, tumor necrosis and hemorrhage were readily seen. Tumor cells showed complete loss of INI1 (SMARCB1) nuclear staining, demonstrated strong and diffuse positivity for TLE-1, FLI-1 and glypican 3, patchy positivity for CD99, cytokeratin, SALL4, LIN 28, EMA and S100, and were negative for PHOX2B, inhibin, calretinin, synaptophysin, chromogranin, WT-1, NKX2.2, GFAP and desmin. The OncoKids NGS panel revealed biallelic frameshift mutations in the SMARCB1 gene (c.673delG and c.683dupT) while CMA did not reveal pathogenic copy number aberrations. The extrarenal SMARCB1-deficient tumors, especially the epithelioid sarcomas, typically have deletions (often homozygous). There was no evidence of metastasis.

Conclusion: The histologic, immunohistochemical and molecular findings support a diagnosis of MRT, albeit with an unusual age, location and mutations. Moreover, although not of CNS origin, the “teratoid” histological features of this case resemble CNS atypical teratoid rhabdoid tumor. The unusual features of this case expand the clinicopathologic and molecular spectrum of MRT.

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Correlation between Cytology and Surgical Pathology in Pediatric Thyroids of PTEN-Hamartoma Tumor Syndrome

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Background: Phosphatase and tensin homolog (*PTEN*) hamartoma tumor syndrome (PHTS) encompasses a group of disorders in which there are germline inactivating mutations of the *PTEN* gene on chromosome 10; these include the Cowden, Bannayan-Riley-Ruvalcaba, and Proteus-like syndromes. Patients with PHTS have an increased lifetime risk of various cancers including pediatric thyroid cancers. We report our institutional experience with the outcomes of pediatric patients with PHTS who underwent fine needle aspiration (FNA) of thyroid nodules as part of cancer screening and had subsequent thyroidectomy.

Methods: CoPath, Epic Beaker, and Epic databases were accessed for partial and total thyroidectomies with prior FNAs performed on patients with a history of PHTS. The FNA was performed by interventional radiologists with rapid on-site evaluation of the smears by a pediatric pathologist. Gross and microscopic examination was performed on the thyroidectomy specimens with the incorporation of immunohistochemical analysis into the final diagnosis. The final diagnosis of the cytology and surgical specimens is correlated retrospectively.

Results: Eight patients with *PTEN* mutations who had undergone FNA biopsy followed by thyroidectomy for thyroid nodules were identified in our institution. Five patients were previously diagnosed with a PHTS, and two patients with negative PTEN immunohistochemical staining are currently undergoing further workup. The eight patients had the following FNA diagnoses: 3 benign, 3 atypia of undetermined significance (AUS), and 2 suspicious for follicular neoplasm. One patient underwent 2 FNA procedures; both of which were benign. The two cytology specimens diagnosed as suspicious for follicular neoplasm had subsequent thyroidectomy with microcarcinoma composed of follicular variant of papillary thyroid carcinoma with multiple follicular adenomas and a thyroidectomy with multiple follicular adenomas. The three cytology specimens diagnosed as AUS corresponded with benign diagnoses including a Hürthle cell adenoma, adenomatous nodules, and multiple adenomatoid nodules with single follicular microadenoma. The six benign cytology specimens corresponded with thyroidectomies with multiple benign lesions: follicular adenomas, adenomatous nodules, and Hürthle cell adenomas. No benign FNA diagnoses were malignant at resection.

Conclusion: At our institution, five patients (62.5%) with PHTS had AUS or suspicious diagnoses by cytology, however only one (12.5%) had a malignant diagnosis at resection. Cytologic examination appears to yield a high rate of atypical or suspicious diagnosis in patients with PHTS who ultimately had benign thyroid pathology. While this is a small study, these results highlight the difficulty of cytologic examination of thyroids in patients with PHTS. This study also shows that thyroidectomy after benign FNA did not reveal unexpected malignancy and may not be necessary unless clinical symptoms are present.