Perinatal Platform Presentation Session 1
Friday, October 23
12:00pm - 12:15pm EDT

01

Examining the Relationship Between Gastroschisis and Placental Fetal Vascular Malperfusion in a Sample of Neonates From Eastern Ontario

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Background: Gastroschisis is a congenital abnormality characterized by herniation of intestinal contents through an abdominal wall defect. Risk factors including maternal smoking and alcohol use during pregnancy have been linked to gastroschisis, despite its unknown pathogenesis. Additionally, young maternal age has been established as a significant risk factor for gastroschisis, though the reason for this remains unclear. Previous work conducted by our group has shown that gastroschisis is associated with placental delayed villous maturation (DVM). The goals of this current study are to identify any additional placental pathologies associated with gastroschisis in order to improve clinical understanding of its pathogenesis, and to determine how maternal and fetal gestational age influence placental pathology in the context of gastroschisis.

Methods: We conducted a retrospective slide review of 30 placentas of neonates with gastroschisis. We also reviewed pathology reports from one control group (n=30) of placentas of neonates with other congenital malformations. Gross and histological data were collected based on a standardized placenta data collection rubric previously developed and validated by our team.

Results: Compared to the control group, gastroschisis was associated with increased placental features of fetal vascular malperfusion (FVM) (60% versus 0%, $p<0.0001$). Gastroschisis was also associated with increased placental villous maldevelopment (77% versus 3%, $p<0.0001$), consistent with findings previously described by our group. Within the gastroschisis cases, there was no significant difference in frequency of FVM ($p=0.46$) or villous malformation ($p=1.0$) in term (GA ≥37 weeks) versus preterm (GA < 37 weeks) cases. Similarly, there was no significant difference in rates of FVM ($p=1.0$) or villous malformation ($p=0.60$) in gastroschisis cases among younger mothers (maternal age <20 years) in comparison to older mothers (maternal age ≥20 years).

Conclusion: Our study demonstrates an association between gastroschisis and placental FVM. Therefore, it supports the notion previously suggested by Cox and Popek: The location of gastroschisis in the ventral body wall predisposes to disruption or compromise of the umbilical cord, which could lead to umbilical vessel thrombosis and downstream findings of FVM. Within our population of neonates with gastroschisis, maternal age and fetal gestational age do not play a significant role in influencing placental pathology.

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02

Formulating a Meaningful and Comprehensive Placental Pathology Classification Which Addresses Multiplicity, Grade and Temporal Distribution of Lesions

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Background: Recent consensus groups have defined and refined the major pathologic categories in the placenta; however, pathologists are often faced with the daunting task of explaining the significance of numerous placental lesions in different anatomic compartments and of different grades or chronicity in a single placenta. The aim of this study was to use a large delivery cohort to define overlapping patterns of placental pathology and determine meaningful phenotypes associated with small for gestational age (SGA) infant and preterm birth (PTB).

Methods: We extracted demographic characteristics, birth outcomes, and the final diagnosis of placental pathology reports from the medical records of singleton live births at a single institution between January 2009 and March 2018. Placental gross and histologic lesions were grouped into four major categories: acute inflammation (AI), chronic inflammation (CI), fetal vascular malperfusion (FVM), and maternal vascular malperfusion (MVM). Within each category, lesions were classified as not present, low grade, or high grade. Additional other chronic pathologies, such as massive perivillous fibrin deposition, were considered as a single combined group. 84 pathology profiles were identified based on all possible combinations of the pathologic categories and their grades. An SGA neonate had a birthweight percentile <10th percentile for gestational age and sex and PTB was delivery <37 weeks gestation.

Results: Of the 19,027 singleton live births, 25% were preterm and 16% were SGA. 21 placental phenotypes were derived from the 84 pathology profiles by collapsing those with equivalent odds ratios (ORs) for SGA and similar distributions across early (<34 weeks) and late (34-36 weeks) PTB. The phenotypes with the highest risk for SGA (OR>10) had either multiple high grade chronic pathologies (OR=15.4), high grade FVM with low grade CI and/or MVM (OR=14.4), or high grade MVM (OR=10.2). Moderate ORs (4-10) were observed for low-grade MVM, other chronic pathology, and high-grade FVM with or without low-grade AI. Mild ORs (<4) were observed for high-grade CI without low-grade MVM and low-grade FVM or CI. When the prevalence of the placental phenotypes were compared between early and late PTB, early PTBs were more likely to have high-grade MVM, high-grade AI with low-grade chronic pathologies, or high-grade AI alone. Late PTBs were more likely to have high-grade CI without AI, low-grade chronic pathologies without AI, low-grade AI alone, or to be histologically normal.

Conclusion: We propose a comprehensive and meaningful placental phenotypic categorization (Freedman-Ernst placental phenotype) which encompasses combinations of acute inflammatory, chronic inflammatory and vascular pathology and can provide correlations with birth outcomes such as SGA and PTB.

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03

Examining the Presence and Number of Placental Lesions on Adverse Pregnancy Outcomes in a Sample of Oocyte Donation Versus In Vitro Fertilization Patients

S Dancey*[1]*, E Mery*[1]*, A Esteves*[1]*, I Oltean*[2]*, L Hayawi*[2]*, D El Demellawy*[2]*; [1]University of Ottawa, Ottawa, Ontario; [2]Children's Hospital of Eastern Ontario, Ottawa, Ontario

Background: Approximately 48.5 million couples worldwide are affected by infertility, resulting in increased use of assisted reproductive technology (ART) including in vitro fertilization (IVF) and oocyte donation (OD). Unfortunately, these therapies are associated with heightened risk of placenta-mediated diseases. To date, a comprehensive analysis of the histopathological lesions associated with ARTs has not been conducted in a population affected by placental disease. Considering the difference in genetic complements in IVF vs OD, with fetal genome allogeneic to maternal in OD, we hypothesize that immune-driven forms of placental disease are more prevalent in OD-derived pregnancies.

Methods: A retrospective study of placenta pathology findings from 115 women who conceived using IVF or OD was conducted on specimens sent to the Department of Pathology between 2012-2018. Cases with singleton, twin or triplet gestation and a diagnosis of a placenta-mediated disease (intrauterine growth restriction, preeclampsia, HELLP syndrome or gestational hypertension) were included. Cases with gestational diabetes, intrauterine fetal demise or severe preterm birth (<28 weeks) were excluded. Histopathology samples were examined by a perinatal pathologist, blinded to the method of ART used and pregnancy outcome, using a validated synoptic data collection tool to assess presence and severity of 30 placental lesions. Data are presented as the average severity score (± standard deviation). Odds ratios (OR) were calculated for placental pathology categories with IVF as the reference group.

Results: Of the 115 participants, 32 used OD (28%) and 83 used IVF (72%). The median gestational age and maternal age across all cases were 35.71 weeks (IQR = 33.79, 37.14) and 37 years (IQR = 33.00, 41.00), respectively. Maternal vascular malperfusion (MVM) lesions had an average severity score of 2.88 (±1.56) in the OD group and 2.49 (±1.73) in IVF (p=0.05). Villitis of unknown etiology (VUE) lesions demonstrated a significant difference between groups [OD= 0.53 (±0.84); IVF= 0.20 (±0.56), p=0.017]. Cases with OD conception were also more likely to demonstrate more severe placental damage with increased total placental pathology score [OR = 6.71 (CI = 1.89-23.80), p=0.0032].

Conclusion: Our results show that OD, compared to IVF, is associated with a higher degree of placental damage; specifically, an increase in MVM lesions. Our hypothesis of heightened maternal-fetal interface immune disturbance may be supported by the increase of VUE lesions in the OD group compared to IVF. Our results also suggest that there may be additional underlying factors that contribute to the pathological lesions observed in OD placentas, which extend beyond the immune mismatch hypothesis.

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04

Placental Cell-specific Extracellular Vesicle Profiles from Syncytiotrophoblasts and Extravillous Trophoblasts in the First Trimester

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Background: Placental extracellular vesicles (EVs) are the subject of intense interest because they reflect relative placental health and provide insights into placental:maternal signaling. To date, most studies have focused on placental alkaline phosphatase (PLAP) positive EVs either by direct imaging or inference derived from size fractionation. We hypothesized that multiplexing multiple antibody markers on each EV would increase PLAP profile specificity and provide insights into relative contributions from syncytiotrophoblasts and extravillous trophoblasts (EVTs) into the maternal circulation during the first trimester.

Methods: Retrospective analysis of banked platelet poor plasma uniformly collected, processed, and frozen from 20 Caucasian women collected at 6, 8, and 10 weeks' gestation. Antibodies were validated using histologic sections to characterize syncytiotrophoblasts (PLAP/CD66f/CD63), EVTs (PLAP/HLA-C/E-cadherin/CD63), and spiral artery "plug" cells (PLAP/CD56/E-cadherin/CD63). Cell- and size-specific EVs were imaged and quantitated per ul of plasma using nanoscale high resolution flow cytometry on a FacsAria Fusion (BD Biosciences) validated by our group. All samples were run in duplicate in a single batch. Plasma samples were simultaneously stained for CD41/CD61/CD9 platelet EV and CD31+/CD41- endothelial EV internal controls present in all plasma samples in the detectable range. Male plasma and stained 0.1um PBS and EV depleted plasma served as negative controls. EV size was estimated relative to Megamix polystyrene beads (100nm-900nm in size). Known quantities of flow sorted 200nm beads were used as sample dilution buffer to serve as concentration controls to normalize test volumes.

Results: Similar to others, we observed the greatest number of PLAP+ EVs/maternal plasma volume at 6 weeks gestation. Syncytiotrophoblast counts trended downward from 6-10 weeks ($p<0.05$) as did CD56+ plug cell EVs. In contrast, HLA-C+ EVT EVs represented the majority of PLAP+ events and counts remained constant from 6-10 weeks. Platelet and endothelial EVs were also constant.

Conclusion: Multiplex nanoscale flow cytometry provides a method to examine placental cell-specific EV profiles in maternal plasma, which we suspect may vary relative to uteroplacental blood flow and pregnancy outcome.

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1:00pm - 1:15pm EDT

05

Abnormal Placental Pathological Findings and Adverse Clinical Outcomes of Oocyte Donation

I Oltean[1], *C Rozon[2], J Clancy[3], Y Liao[4], S Wen[4], K Fung-Kee-Fung[3], D El Demellawy[5], A Esteves[6];* [1]Children's Hospital of Eastern Ontario, Ottawa, Ontario; [2]Department of OBGYN, University of Ottawa, Ottawa, Ontario; [3]Division of Maternal Fetal Medicine, Dept. of OBGYN, University of Ottawa, Ottawa, Ontario; [4]OMNI Research Group, Dept. of OBGYN, University of Ottawa, Ottawa, Ontario; [5]Dept. of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, Ontario; [6]Faculty of Medicine, University of Ottawa, Ottawa, Ontario

Background: While Canadian trends demonstrate increasing use of assisted reproductive technologies (ART), these pregnancies have been associated with adverse obstetrical and neonatal outcomes, independent from the risk of delivering multiples. Pregnancy achieved by oocyte donation (OD) is a unique form of ART in which the gestational carrier is exposed to a completely allogeneic fetus and may be associated with unique complications when compared to non-OD ART due to greater maternal-fetal antigenic incompatibility. It was hypothesized that a heightened inflammatory response stemming from this incompatibility would manifest as placental pathologies and adverse clinical outcomes. The objective of this study was to correlate maternal and fetal outcomes with placental pathologies in a Canadian context.

Methods: This retrospective study included patients who achieved pregnancy by OD and non-OD ART and delivered at The Ottawa Hospital (TOH) between 2011 and 2018. A total of 355 pregnancies (24% OD) and 553 fetuses (23% OD) were included. Data describing maternal demographics, obstetrical outcomes, neonatal outcomes, and placental pathology were collected and analyzed.

Results: While results demonstrated increased frequency of preeclampsia, gestational hypertension, and gestational diabetes, they were not statistically significant when adjusted for maternal age, parity, plurality, and BMI. Further, there were no significant observed differences in adverse neonatal outcomes. Placental pathology data demonstrated significantly increased rates of placenta accreta (p<0.001), chronic deciduitis (p=0.02), maternal vascular malperfusion (p=0.02), and fetal vascular malperfusion (p=0.02) in the OD ART group suggesting a chronic inflammatory response and abnormal endometrial milieu.

Conclusion: In support of maternal-fetal antigenic incompatibility, our study demonstrates an increased risk of placental pathological findings and pregnancy associated diseases related to systemic immuno-activation in OD pregnancies. We expect that our findings will be utilized in evidence based clinical decision making for patients seeking to achieve pregnancy as need for donor oocyte treatments continues to rise.

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2:15pm - 2:30pm EDT

06

Preterm Infant Skin Structure Is Qualitatively and Quantitatively Different from that of Term Newborns

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Background: The immature skin of preterm infants is uniquely vulnerable to injury, including pressure injury and chemical injury, and with the increasing survival of preterm infants of very young gestational age, these vulnerabilities are heightened. Pressure injuries are currently staged based on bedside evaluation of injury depth and involved structures. However, this system was developed in and for adults, raising questions about whether it is relevant in preterm infants. To begin addressing this question, we sought to qualitatively and quantitatively describe the patterns of skin development in preterm infants.

Methods: Skin samples taken at autopsy were examined for 48 live born preterm infants, 15 term infants, and 8 infants and children 9-24 months old. Preterm infants were born at 18+ to 36 weeks, and died at 18+ to 50 weeks corrected gestational age (CGA). H&E stained slides of skin were photographed and measured digitally. Quantitative variables included thickness of the stratum corneum, epidermis, and dermis, and number of cell layers in the epidermis. Qualitative features examined included stratum corneum, rete ridges, and hair follicles and hair shafts.

Results: Among preterm infants, the epidermis and adnexae showed reproducible patterns of maturation. Compact keratin appeared beginning at 21-22 weeks. Basketweave keratin appeared first around hair follicles, at 21-29 weeks, and then became more generalized from approximately 28 weeks onward. Rete ridges were absent in all very young infants and some older infants, but frequently present at 30 weeks CGA and later. Hair follicles were present in all cases, and hair shafts appeared beginning at 21-22 weeks. Skin morphometry showed an age-dependent increase in epidemal and dermal thickness. Epidermal thickness was similar between preterm infants with CGA near 40 weeks and term neonates. Infants who survived ≤7 days generally had thicker dermis than those with longer survival time, even when adjusted for CGA.

Conclusion: Skin development in preterm infants has several reproducible milestones. Most significantly, basketweave keratinization, like keratinization generally, begins in hair follicles and subsequently becomes more generalized by about 28 weeks. Around 30 weeks, rete ridges begin to appear. These changes may confer improved barrier function, with implications for use of topical chemicals such as chlorhexidine. The findings also highlight challenges in evaluating pressure injuries in very preterm infants. A stage 3 pressure injury (full thickness loss of skin), for instance, may <1 mm deep. A better understanding of the qualitative and quantitative developmental histology of skin in preterm infants will help to drive evidence-based policy to prevent and manage skin injuries in the NICU.

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2:30pm - 2:45pm EDT

07

The Placental Protein Expression Pattern of the SARS-CoV-2 Receptor ACE2 and Serine Proteinase TMPRSS2 Suggest a Protective Mechanism Against Infection

J Hecht[1], B Quade[2], V Deshpande[3], M Mino-Kenudson[3], D Ting[3], N Desai[3], B Dygulska[4], T Heyman[4], C Salafia[5], D Shen[6], S Bates[3], ***D Roberts[3]***; [1]Beth Israel Deaconess Medical Center, Boston, Massachusetts; [2]Brigham and Women's Hospital, Boston, Massachusetts; [3]Massachusetts General Hospital, Boston, Massachusetts; [4]New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York; [5]Placental Analytics, New Rochelle, New York; [6]Kaiser Permanente Downey Medical Center, Downey, California

Background: The rarity of placental infection by SARS-CoV-2 suggests the presence of protective measures. SARS-CoV-2 requires coexporession of its receptor, ACE2, and the serine proteinase TMPRSS2 for cellular infection. Both are expressed in the placenta but their protein expression pattern has not been demonstrated to date.

Methods: 19 placentas from women with PCR proven SARS-CoV-2 infection were examined for SARS-CoV-2 expression by RNAish and immunohistochemistry (IHC) and for ACE2 and TMPRSS2 by IHC. Gross and histopathology were also reviewed. Two sets of controls were used: "normal controls" - 122 placentas examined solely for GBS exposure (no other indication for examination) delivered from 2000-2004; and "abnormal controls" - 130 placentas from neonates with a clinical diagnosis of HIE delivered from 2000-2019. The control placentas were reviewed for gross and histopathology.

Results: 2 cases showed placental infection with viral RNA the villous syncytiotrophoblast (ST) and cytotrophoblast (CT) in a patchy distribution in 1 and only focally in the other. The infant with the patchy infection was SARS-CoV-2 PCR positive at 24 hours, the infant with only focal infection was PCR negative. None of the other placentas showed viral infection. All placentas showed robust expression of ACE2 in the trophoblast. The ST and CT expression was membranous and In most cases ST expression was polarized-strongest, and in many cases only present, on the villous stromal side of the ST. TMPRSS2 was weakly expressed in the placental endothelial cells. Hofbauer cells were negative for both.

We did not find a an increase in maternal or fetal vascular malperfusion (MVM or FVM) over controls.We saw MVM at 25%, FVM at 20%, acute chorioamnionitis at 30%, inflammatory pathologies (1 case each of ungradable VUE, intervillositis, Hofbauer cell hyperplasia) at 15%, all within published prevalences and similar to our controls.

Conclusion: We did not find increased prevalence of MFM, FVM, infectious, or inflammatory pathology above published our our sets of controls as other have, perhaps due to small sample size.

SARS-CoV-2 infection of the placenta is rare and vertical transmission, if it occurs, is even rarer. One mechanism for this is the rare occurrence of maternal SARS-CoV-2 viremia. Another mechanisms might be the unfavorable expression ACE2 and TMPRSS2 . We show that their expression is uniquely distinct: ACE2 in the tropohobast and TMPRSS2 in the endothelium. Although we did not detect coexpression we cannot rule

out that the vascular-syncytial membranes might coexpress ACE2 and TMPRSS2. We also show that ACE2 expression is polarized in most cases away from the maternal vascular space thereby perhaps limiting SARS-CoV-2 access to ST infection.

Perinatal Platform Presentation Session 2
Friday, October 23
2:45pm - 3:00pm EDT

08

The Value of Ancillary Testing in Autopsies for Amniotic Fluid Infection/Inflammation Syndrome

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Background: Amniotic fluid infection/inflammation syndrome (AFII) is a common cause of premature delivery and demise. Autopsies in the setting of AFII may include up front testing like microbiological studies and genetic analyses. Ordering ancillary testing at the time of autopsy can reduce time to report completion but has drawbacks including increased workload, increased cost, and false or variant results that complicate autopsy interpretation. Review of the use of ancillary testing in AFII autopsies may identify areas to improve practice.

Methods: This is a retrospective quality assurance study. Research ethics board review is waived. Autopsy reports between Aug. 1 2014 and Dec. 31 2019 with “amniotic fluid infection” or “chorioamnionitis” in the report are retrieved from a Women’s Hospital pathology department. Reports are extirpated if: AFII is not the cause of demise, termination for developmental or genetic defect, non-iatrogenic traumatic rupture of membranes, AFII associated with chronic abruption-oligohydramnios sequence, no internal fetal examination, intrauterine demise without fetal evidence of AFII, or fetus is received in formalin. Reports passing these exclusionary criteria are assessed for features of AFII, ancillary studies performed, and the contribution of ancillary studies to the final autopsy findings.

Results: 304 reports passed the exclusionary criteria. Clinical presentations include spontaneous delivery (51%), PPROM (29%), IUFD (9%), and incompetent cervix (8%). Cultures were performed on at least one site in 53% of total cases and yielded at least one positive result in 43% of those cases. The most common bacteria identified is Group B Streptococcus. Culture and histology were concordant in 6%, culture positive and histology negative in 33%, and culture negative and histology positive in 6%. Fungal culture was performed in 8% of cases with 1 case positive. PCR for cytomegalovirus was performed in 14% of total cases; all were negative. Genetics was performed in 52% of total cases of which 45% returned a normal result, 4% failed, and 3% yielded a non-normal result. Other studies, such as electron microscopy, were not performed.

Conclusion: Bacterial culture can add information on infectious etiology in the setting of AFII, particularly by identifying GBS which may cause recurrent pregnancy loss. It would be more efficient to defer genetic and viral testing in the absence of a strong indication at the time of autopsy for up front testing. Although this study is not prospective and does not take into account presentations that may be similar to AFII, like acute abruption, AFII is frequently suspected at the initiation of an autopsy and these findings can help improve the efficiency of ancillary testing in this setting.

Perinatal Platform Presentation Session 2
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3:00pm - 3:15pm EDT

09

Placental Pathology in a Population of Pregnant Women Under Investigation for COVID-19 Delivering at a Tertiary Care Hospital

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Background: To determine the prevalence of infection and to describe the histopathologic findings in the placentas of women under investigation for COVID-19 admitted for delivery to our tertiary care hospital during the pandemic.

Methods: Pregnant women considered as persons under investigation (PUI) for COVID-19 by our institution's protocol and who delivered between April 8 and June 11, 2020, were identified. Placentas were sent to Pathology for gross and microscopic examination. Correlation with maternal COVID-19 test status was performed.

Results: Nine placentas from patients considered PUI for COVID-19 were received in our department and fixed in formalin according to our modified protocol for potential COVID-19 positive specimens. Of note, the results of the maternal COVID-19 tests were not available at the time of pathologic examination. Eight were third trimester placentas with live births; one was a third trimester twin placenta with one live birth and one stillbirth. Pathologic findings included acute chorioamnionitis (4/9), perivillous fibrin deposition (3/9), placental infarct (1/9) and intervillous thrombus (1/9). Immunohistochemical study for COVID-19 was negative in all placentas. Maternal COVID-19 test results (received subsequently) were positive in 4/9 cases. These four COVID-positive cases showed: acute chorioamnionitis (2), intervillous thrombus (1) and placental infarct (1).

Conclusion: In our limited series, the prevalence of COVID-19 infection in pregnant women considered PUI who delivered at our institution is 44%. This significant percentage warrants the use of our modified fixation protocol for potential COVID-19 positive specimens when handling these placentas. In our study, not all placentas from COVID-19 positive women showed features of maternal vascular malperfusion, as described in other series; and two placentas showed acute chorioamnionitis. Studies of larger numbers of placentas from pregnant women with COVID-19 are needed to fully understand the pathologic involvement of the placenta in this disease.

Perinatal Platform Presentation Session 2
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10

Bacterial 16SrRNA PCR in the Extraplacental Membranes with Histologic Acute Chorioamnionitis: Comparison of Term and Preterm Placentas.

A Clarke-Brodber[1], *S Das[1], K Mangold[1], L Ernst[1];* [1]NorthShore University HeathSystem, Evanston, Illinois

Background: Despite the high prevalence of acute chorioamnionitis and evidence of microbial invasion of the amnionic sac, the incidence of early onset neonatal sepsis, defined by a positive blood culture, is low. Bacteria are only rarely identified on the extraplacental membranes in acute chorioamnionitis by histology, but we hypothesized that sensitive molecular techniques could identify bacteria more readily and that the bacterial profile would differ between preterm and term chorioamnionitis.

Methods: We selected 19 preterm (<37 weeks gestation) and 20 term (≥ 37 weeks gestation) placentas with histologic acute chorioamnionitis (maternal acute inflammatory response (MIR) and fetal acute inflammatory response (FIR) ≥2) from the pathology database. The presence of bacterial organisms on the membranes by H&E stain or Brown & Hopps stain was noted. DNA was extracted from the FFPE tissue block of the membranes and a 500 bp fragment of the bacterial 16SrRNA gene was sequenced using universal primers by Sanger sequencing method.

Results: Bacterial organisms were seen by PCR in 17/39 (44%) cases; 5/19 (26%) preterm and 12/20 (60%) term (P=0.034). Bacteria were seen by histology in 10/39 (26%) cases; 6/19 (32%) preterm and 4/20 (20%) term. Most of the PCR products were mixed bands on electrophoresis prior to Sanger sequencing with only three pure organisms on analysis of FASTA files and BLAST query on NCBI: Lactobacillus iners in one preterm infant (Fusobacterium-like species on histology), Staphylococcus epidermidis and Propionobacterium acnes in two term infants. Four preterm neonates died shortly after birth, two with bacteria on histology only one of which showed a mixed PCR product. Only 1/39 (2.5%) neonates had a positive blood culture (Streptococcus viridans) but was negative for bacteria by PCR and histology. Stage of MIR and FIR did not differ between PCR positive cases and PCR negative cases. PCR positivity did not correlate with the histologic finding of bacteria on histology. Among the 35 living neonates, 5 received a 7 day course of antibiotic (presumed sepsis). 4/5 (80%) had bacteria on histology vs only 4/30 (13%) with bacteria on histology without presumed sepsis (P=0.006). Only 1/5 (20%) neonates with presumed sepsis was PCR positive.

Conclusion: 16SrRNA gene PCR identified pure and mixed bands of bacterial organisms in the extraplacental membranes with acute chorioamnionitis, more commonly in term placentas than preterm placentas. However, correlation with positive neonatal blood culture, neonatal death, bacteria on histology, and MIR or FIR is poor. Histologic presence of bacteria correlated best with presumed sepsis in the neonate. A major caveat in our study is the use of FFPE tissue. Further investigation is needed to assess this technique in acute chorioamnionitis.

Pediatric Platform Presentation Session 3
Saturday, October 24
10:50am - 11:05am EDT

11

Correlation of Fecal Calprotectin Levels with Histologic and Endoscopic Findings in Pediatric Inflammatory Bowel Disease

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Background: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract with a relapsing and remitting course. Remission measured with clinical indices frequently do not correlate with endoscopic remission in children or adults. Fecal calprotectin (FC) is a non-invasive marker of intestinal inflammation. The aim of our study was to examine the association of quantitative FC levels with endoscopic and histologic severity as well as differences in FC in IBD patients with endoscopic remission compared to controls.

Methods: We reviewed pediatric patients who had FC done between 30 days and 1 day prior to colonoscopy at our institution between 2014 and 2018. Endoscopically, patients with IBD were graded using the simple endoscopic score for Crohn's disease (SES-CD) or Mayo UC score. Histologic slides were evaluated using the Geboes method and assigned a score of 0-5.

Results: 331 patients were included in the study and 107 had IBD. When assessing endoscopic scoring, median FC was lowest in those with no disease (181 ug/g) and highest in severe disease (921 ug/g), with significant difference between no disease and moderate and severe disease (p=0.019, 0.003), and between mild and severe disease (p=0.012). When assessing histology, median FC was lowest with no disease (328 ug/g) and highest in severe disease (895 ug/g), with significant difference between no disease and moderate and severe disease (p=0.021, 0.018). The control population had a significantly lower median FC than the IBD population with endoscopic remission (43 ug/g vs 181 ug/g, p=0.018).

Conclusion: There was significant difference between FC values when examining disease severity. Values for IBD patients in endoscopic remission were significantly different than the control population. Overall, FC showed good correlation with disease severity on endoscopic and histologic assessment in pediatric IBD patients. While endoscopic surveillance and biopsy is still the gold standard for diagnosis and assessing disease severity in IBD patients, FC may be a noninvasive and more cost-effective tool for assessment.

Pediatric Platform Presentation Session 3
Saturday, October 24
11:05am - 11:20am EDT

12

Cytogenetic Analysis of Ovarian Teratomas in Children

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Background: Teratomas are the most common tumors in the ovary during childhood. Previous studies suggested that they may be derived from germ cells at any developmental stage from pre-meiotic oogonia through meiotic oocytes to mature, post-meiotic ova. The majority of mature teratomas reveal normal karyotypes and immature teratomas show higher frequency of chromosomal abnormalities.

Methods: We analyzed fresh tissue samples from 23 primary ovarian teratomas and 3 extragonadal deposits using whole genome single nucleotide polymorphism (SNP) array and karyotype.

Results: Patients age ranged from 5 to 14 years. We identified 17 patients with mature teratomas and 6 with immature teratomas. Five of the latter contained variable amounts of Yolk sac tumor (YST). One patient had bilateral immature teratomas with YST. Whole genome SNP array detected five patterns of copy neutral loss of heterozygosity (CN-LOH). Failure of meiosis I (Type I error) with CN-LOH in the p arm and/or q arm of chromosomes without spanning centromeres occurred in 9 cases, Type II error characterized by homozygosity spanning centromeres in 1 case, Type III error with homozygosity of the entire genome via endoreduplication of a haploid ovum in 2 cases, Type IV error with no acquired CN-LOH in 4 cases, and Type V error with both meiotic I and meiotic II non-disjunction in 7 case. Among the cases with Type V error, one case had almost identical number of chromosomes showing meiotic I or II non-disjunction, and 6 of the cases each had a single chromosome showing meiotic I or II non-disjunction while the remaining chromosomes showed meiotic II or I non-disjunction respectively. The three extraovarian deposits revealed same CN-LOH pattern as the primary teratoma. One case lacked the del(3q) observed in the primary teratoma, which may reflect tumor heterogeneity. Abnormal karyotypes were observed in 3 of the mature teratomas [i(18q), +7, +8, respectively], and in 1 of the immature teratomas [+3, del(3q), +12].

Conclusion: To our knowledge, this is the largest study of ovarian teratomas in children using whole genome SNP array. Our findings suggest that abnormal karyotypes and consecutive meiotic I and II errors are common in ovarian teratomas.

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Saturday, October 24
11:20am - 11:35am EDT

13

Mycophenolate Mofetil Hepatotoxicity Associated with Mitochondrial Abnormality in Liver Transplant Recipients and Mice Treated with MMF

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Background: Recognition of Drug-induced liver injury (DILI) can be challenging because DILI displays diverse, often nonspecific laboratory and histopathologic changes. Mycophenolate mofetil (MMF) is a widely used immunosuppressant agent. Rare cases of MMF hepatotoxicity have been reported in non-transplant patients and renal transplant recipients but these reports have minimal histologic and no ultrastructural findings. This is the first study describing the detailed histology and ultrastructure of MMF hepatotoxicity.

Methods: Four liver-transplant recipients (Case 1-4) were clinically suspected to have MMF hepatotoxicity. Case 1-3 (2 females and 1 male; 3-17 years) had multiple biopsies for liver function test (LFT) abnormalities. Case 4 (female; 14 years) had a surveillance biopsy as per institutional protocol. Electron-microscopic examination (EM) was requested on Case 1-3 for unexplained, persistent LFT and histologic abnormality despite ongoing medical therapy and Case 4 for unexplained histologic abnormality despite a stable clinical course. To confirm the pathologic changes seen in human liver allografts, livers from MMF-treated and untreated mice were also reviewed.

Results: While the allograft biopsies showed nonspecific histologic changes, EM revealed unequivocal mitochondrial morphological abnormality similar to that seen in primary and secondary mitochondrial disorders. In Case 1 and 2, LFTs improved after stopping and reducing MMF, respectively. In Case 3, pre- and post-MMF treatment biopsies were performed and only post-MMF biopsy demonstrated mitochondrial abnormality. Mitochondrial abnormality in Case 4 was subclinical. In the mouse study, image analysis using EM revealed various mitochondrial stress changes in the livers from the MMF-treated mice; number of mitochondria and lipid droplets and degree of mitochondrial pleomorphism were significantly increased in hepatocytes in the MMF-treated group compared with those in the untreated group ($p < 0.0001$).

Conclusion: Although MMF is safe for majority of patients, MMF could stress mitochondria and the stress may trigger more severe mitochondrial abnormality in a small subset. MMF hepatotoxicity should be considered for MMF-treated patients with unexplained, persistent LFT abnormality and nonspecific histology. EM can play a critical role in these cases.

Pediatric Platform Presentation Session 3
Saturday, October 24
11:35am - 11:50am EDT

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"Viral" Virtual Education: Constructing a Virtual Pediatric Lab Medicine Elective for Medical Students and Trainees

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Background: In March 2020, COVID-19 began its spread across the United States. Due to limited personal protective equipment and concerns for learner safety, many medical schools ceased offering clinical rotations. As such, our affiliated medical school called for the rapid implementation of virtual electives for medical students. Herein, we describe construction of a virtual pediatric laboratory medicine elective designed to improve learner understanding of the role of the laboratory in patient care, doing so within COVID-19-related restrictions.

Methods: To develop the course curriculum, we first examined content and structure of current elective offerings from our pathology department. We reviewed the literature for previously published clinically-focused pathology/lab medicine curricula and courses. Additionally, we assessed recommendations for laboratory medicine educational topics for medical students by various professional societies within pathology and laboratory medicine. We sought insight from clinical educators in the department of pediatrics regarding observed/perceived gaps in knowledge among medical students and pediatric residents to identify additional targets for education. Finally, we gathered information regarding the effectiveness/implementation of different teaching modalities to incorporate into the curriculum.

Results: A four-week curriculum in anatomic (AP) and clinical pathology (CP) was developed. Instructional methods included video tours of the labs, interactive didactic sessions/discussion via computer video conferencing (CVC), interactive "sign out" with attendings via CVC using microscope photography software, independent virtual slide review, video lectures, and independent literature review. AP topics included overview of tissue processing, pediatric surgical pathology sign out, pediatric/perinatal autopsy overview/case studies, and congenital heart anomaly review. CP topics included pediatric-focused clinical chemistry, microbiology, transfusion medicine, hematopathology, molecular pathology, and quality assurance. Assessment methods included pre- and post-tests and a case-based presentation highlighting the role of AP and CP in diagnosis and management. Pre- and post-rotation surveys were also incorporated for learner self-assessment of knowledge gaps and gains.

Conclusion: We present one strategy for development of a virtual pediatric-focused lab medicine elective for medical students. Such rotations can be utilized at remote campuses, can be readily adjusted to suit needs of resident learners, and can be easily implemented in the changing COVID environment. Rotations such as this can enhance understanding of the role of the laboratory in pediatric medicine while providing flexibility and a safe environment for learners.

Pediatric Platform Presentation Session 3
Saturday, October 24
11:50am - 12:05pm EDT

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PLAG1 Expression May Represent a Common Feature of Mammary-type Myofibroblastoma

M Arnold[1]*, A Al-Ibraheemi*[2]*, S Chen*[3]*, M Conces*[4]*, J Davis*[5]*, I John*[6]*, S Koo*[4]*, D Parham*[7]*, E Rudzinski*[8]*, G Somers*[9]*;* [1]Children's Hospital Colorado, Aurora, Colorado; [2]Boston Children's Hospital, Boston, Massachusetts; [3]Rhode Island Hospital, Providence, Rhode Island; [4]Nationwide Children's Hospital, Columbus, Ohio; [5]Oregon Health & Science University, Portland, Oregon; [6]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [6]None, Little Rock, Arkansas; [8]Seattle Children's Hospital, Seattle, Washington; [9]The Hospital for Sick Children, Toronto, Ontario

Background: Mammary-type myofibroblastoma is a rare soft tissue tumor that is associated with loss of Rb but is not known to occur in association with gene fusions. We encountered a case of mammary-type myofibroblastoma presenting as a pelvic mass in a teenage female. Genetic analysis identified a COL3A1-PLAG1 gene fusion. To determine whether this gene fusion is a recurrent abnormality in mammary-type myofibroblastoma, we analyzed additional cases of mammary-type myofibroblastoma using partner-agnostic RNA sequencing and PLAG1 immunohistochemical staining.

Methods: Using the partner-agnostic Illumina Trusight assay, 8 additional cases of mammary-type myofibroblastoma were identified from 2 other institutions and were tested for a panel of possible gene fusions involving 1382 genes including *PLAG1*. Using the anti-PLAG1 monoclonal antibody 3B7, PLAG1 immunohistochemical staining was performed on 8 of the 9 mammary-type myofibroblastomas and 11 cases of 4 other entities in the differential diagnosis. The histology of representative H&E stained sections was reviewed by five of the authors, blinded to the PLAG1 results.

Results: RNA sequencing of the 8 additional cases of mammary-type myofibroblastoma did not identify gene fusions. Immunohistochemical staining for PLAG1 showed diffuse nuclear reactivity in 6 of 8 cases tested (75%), including the index *PLAG1* fusion-positive case. The PLAG1-negative tumors were highly cellular yet showed overlapping histologic features with the positive cases. In comparison, patchy nuclear PLAG1 reactivity was seen in 3 of the 11 (27%) tested cases of histologic mimics (atypical lipomatous tumor = 0/2, cellular angiofibroma = 1/2, spindle cell lipoma = 1/5, solitary fibrous tumor = 1/2).

Conclusion: Though *PLAG1* gene fusions do not appear to be frequent in mammary-type myofibroblastoma, immunohistochemical staining for PLAG1 preliminary suggests that PLAG1 expression may be a common feature. In our data, the difference in frequency of PLAG1 expression between mammary-type myofibroblastoma and histologically similar tumors did not reach statistical significance (p=0.07). Examination of additional mammary-type myofibroblastomas is required to determine whether PLAG1 expression is a common biologic feature and a potentially useful diagnostic tool.

Pediatric Poster
Virtual Poster Viewing

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Sarcoma Pediatric Pathology Research InTErest group (SPPRITEs)

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Background: Although the field of pediatric pathology remains one of the last bastions of general pathology practice, a successful academic career continually requires a push towards further subspecialization. As the primary academic society for pediatric pathology in North America, the Society for Pediatric Pathology (SPP) brings together pathologists across the globe, many of whom share similar academic subspecialty interests. The collegial membership provides fertile ground for the creation of small subspecialty research interest groups. Herein, we describe the creation of SPPRITEs (the Sarcoma Pediatric Pathology Research InTErest group) as a model to promote academic pediatric pathology and further discovery in rare pediatric diseases.

Methods: Models of successful pathology subspecialty interest groups exist both within SPP (Perinatal Group) and outside of SPP (eg. Gnomes and Elves in hepatopathology). Based on published descriptions detailing how such groups may be successfully formed, we identified a group of pathologists with research interests in soft tissue neoplasia and multidisciplinary experts in pediatric sarcoma oncology and surgical oncology. The group was restricted initially to 10 members to facilitate early success and collaborative engagement. To begin, SPPRITEs defined its purpose and developed bylaws to define membership, leadership, and principles of research projects, authorship, and intellectual property. The group then developed a forum to share interesting cases, ensuring a mechanism to identify new research projects and involve trainees across member institutions. Finally, SPPRITES successfully applied for modified institutional review board and material transfer agreements at each individual's institution, forming the foundation for present and future work.

Results: Since establishment of bylaws and in person meetings in November 2018 and January 2020, SPPRITEs has had several academic successes. These include abstract platform presentations at the Spring 2019 SPP meeting and the Spring 2020 USCAP meetings, reporting several small case series of rare tumors. These presentations have resulted in one accepted manuscript, and two additional manuscripts are in preparation. Our first collaborative investigational project was also submitted for consideration as an abstract for the Fall 2020 SPP Meeting, and new projects are underway.

Conclusion: Formation of a dynamic subspecialty interest group can promote successful research collaboration amongst institutions, foster career development and advancement for academic pediatric pathologists, and ultimately lead to better patient care. As SPPRITEs develops further, membership will expand. SPPRITEs aspires to become a model for other academic pathology subspecialty interest groups, especially within SPP.

Pediatric Poster
Virtual Poster Viewing

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Predictive Capacity of Histopathology for Post-Operative Complications of Ileal (J) Pouch Procedure in Children with Ulcerative Colitis

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Background: The ileal (J) pouch procedure has been widely used for surgical management of pediatric ulcerative colitis (UC) and is performed by anastomosing the ileum to the anal canal. This procedure aims to reconstruct a functional intestinal tract; however, the post-operative course may show complications. The purpose of this study is to evaluate the predictive capacity of histological parameters for post-operative complications of the J-pouch procedure in pediatric patients with UC.

Methods: A retrospective chart review identified all pediatric patients with UC who underwent a J-pouch procedure at our institution between January 2012 and June 2019. Tissue sections generated from colectomy and J-pouch procedure were graded using histological parameters described in a modified version of the Geboes et al. score and the PROTECT study score. Twenty-two histological parameters assessed at four anatomical sites (colonic and rectal margins, and colonic and rectal segments, excluding margins) were analyzed for association with six common post-operative complications. The correlation between the change in severity of each parameter from colectomy to J-pouch procedure and the length of time between surgeries was also measured.

Results: Thirty-one patients were included in this study, 17 (54.8%) of which developed post-operative complications. At time of UC diagnosis, the median age was 12.9 [IQR: 11.5, 14.6] and the median Pediatric UC Activity Index score was 50.0 [45.0, 60.0; n=23]. Failure to respond to medical treatment was an indicator for J-pouch procedure in 30 (96.8%) cases. Paneth cell metaplasia in the rectum segment at J-pouch procedure was significantly associated with a decreased risk of post-operative complication following J-pouch [OR: 0.0 (0.0, 0.6)]. None of the assessed parameters were significantly associated with an increased risk of post-operative complication. The length of time between surgeries was not significantly different between the complicated and uncomplicated groups (p=0.52).

Conclusion: The histological parameters from the modified Geboes et al. score and PROTECT study score did not exhibit significance in predicting an increased risk of post-operative complications. The time elapsed between colectomy and J-pouch procedure was not found to impact the likelihood of a complicated post-operative course. Our findings differ from a previous study by El Demellawy et al. (2016), which reported an association between UC disease activity at the rectal margin and increased risk of post-operative complications. We believe further studies of larger sample sizes should investigate the value of histopathology for predicting post-operative complications of J-pouch procedure in cases of pediatric UC, which may assist clinicians with improved planning of post-operative management.

Pediatric Poster
Virtual Poster Viewing

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Juvenile Granulosa Cell Tumor – An Important Diagnostic Consideration When Presented with an Ovarian Tumor in Patients with Ollier Disease

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Background: Ovarian granulosa cell tumor (GCT) is a rare type of hormonally active tumor arising from ovarian sex cord stromal cells. Incidence of GCT is 0.4-1.7 cases per 100,000, with <5% of these representing the juvenile form (JGCT). Ollier disease is a rare condition (incidence 1 in 100, 000) marked by multiple benign enchondromas, which can lead to bony deformation and fractures. An association between Ollier disease and JGCT has been documented in the literature.

Methods: We present 2 cases of JGCT associated with Ollier disease, including detailed clinical, histologic, and molecular pathologic findings.

Results: Case 1 was an 11-year-old female with history of right knee enchondroma status-post surgical excision, who presented to the ED with heavy menstrual bleeding. She was initially diagnosed with Ollier disease by knee pain and valgus deformity 2 years prior to the current presentation. She was admitted for management of symptomatic anemia requiring blood transfusion and her examination upon admission was remarkable for a palpable pelvic mass. Ultrasound (US) and CT imaging revealed a large, right ovarian mass.

Case 2 was a 13-year-old female with nonoperative enchondroma of the right middle finger diagnosed 2 years prior, who had an abdominal US as part of an outpatient workup of irregular mensural bleeding and iron-deficiency anemia, which revealed a large, left ovarian mass. After diagnosis of the JGCT, a skeletal survey was performed and revealed previously unknown, asymptomatic enchondromas in the right scapula and wrist leading to diagnosis of Ollier disease.

The ovarian masses measured 21 cm and 16 cm in greatest dimension, respectively. They were encapsulated and confined within the ovary without rupture of the capsule (FIGO stage: IA). Sectioning of the masses showed a tan-yellow, mostly solid cut surface with multifocal cystic areas. The histology of the ovarian masses demonstrated characteristic features of JGCT comprised of granulosa and theca cells that were arranged in solid and follicular patterns. Molecular pathology findings in both cases were significant for an IDH1 p.Arg132Cys (R132C) hotspot mutation consistent with the underlying diagnosis of Ollier disease.

Conclusion: We report 2 cases of JGCT found in teenage females, both of which with R132C mutation, with known diagnoses of enchondromas. It is important for the pathologist to recognize the association of JGCT and Ollier disease in order to arrive at an accurate diagnosis. Specifically, Case 2 demonstrates how a pathologic diagnosis of JGCT can prompt a clinical workup leading to diagnosis of Ollier disease.

Pediatric Poster
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Uncommon Primary Epithelial Malignant Neoplasms of the Mandible

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Background: Malignant neoplasms of the maxillofacial region of children are uncommon and demonstrate an unusual spectrum from familiar to unique tumors. A subset are odontogenic in origin but malignant subtypes are especially rare. Other non-odontogenic malignant tumors are mostly osteosarcoma and Ewing sarcoma and beyond these neoplasms, the list becomes an attenuated one. Along the latter lines, we are presenting two unique primary malignant epithelial tumors presenting in the mandible of 11 and 12 year old children; one of them began as a unicystic ameloblastoma with malignant progression and the other a unique adenocarcinoma whose exact histogenesis remains uncertain but had a fusion transcript involving EWSR1

Methods: Patient 1 (P1): 11-year-old boy with diagnosis of unicystic ameloblastoma of mandible in 2015 presents with a large tumor in the prior resection area in 2019 which showed residual unicystic ameloblastoma in addition to high nested malignant small cell neoplasm, positive for CAM 5.2, CD99 and harbored a *BRAF* V600E mutation and negative for EWSR1 gene rearrangement, consistent with malignant transformation of ameloblastoma. Despite hemimandibulectomy and chemotherapy presents with distant metastasis in 2020. Patient 2 (P2): 12-year-old girl with 5.3 cm expansile solid mass with sclerotic borders in mandible. Wedge biopsy showed an atypical epithelial neoplasm with malignant potential of salivary or odontogenic origin

Results: P1: 8.0 cm, fairly circumscribed mass in the body of mandible demonstrated a poorly differentiated round cell carcinoma (90%) with bone invasion and focal residual areas of unicystic ameloblastoma. P2: 6 cm, vaguely circumscribed mass that demonstrated solid, mixed glandular nests of tumor cells in a background of stroma, positive surgical resection margins; strongly positive for CK7, AE1-AE3, weak and patchy positive for CD99, vimentin. Genomic sequencing revealed EWSRI-YY1 gene fusion.

Conclusion: Ameloblastic carcinoma is a rare primary epithelial odontogenic neoplasm; de novo origin or arise in a pre-existing ameloblastoma and show BRAF mutations as in ameloblastoma. Maligant transformation distinguished by necrosis and infiltration with residual ameloblastoma. This challenging case with its small cell round cell pattern and focal remnant ameloblastoma presented dilemma of second primary neoplasm with Ewing-like features. BRAF positivity and absence of EWSR favored ameloblastic carcinoma. EWSR1-YY1 fusion is a novel fusion marker which has been previously reported in malignant mesothelioma. This is the first case report of this unique gene fusion in a mandible tumor in the pediatric age group. The histologic features are most suggestive of a salivary gland neoplasm of an unclassified type; yet another example in the spectrum of EWSR-related neoplasms.

Pediatric Poster
Virtual Poster Viewing

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Bilateral Sertoli-Leydig Cell Tumors: a Pathognomonic Feature of *DICER1* Syndrome?

***C Hughes*[1];** Vanderbilt University Medical Center, Nashville, Tennessee

****Resident Recruitment Award Presentation***

Background: *DICER1* tumor predisposition syndrome is an autosomal dominant disorder caused by mutations in the *DICER1* gene that encodes an endoribonuclease, resulting in defective microRNA processing. The syndrome is characterized by an increased risk for development of pleuropulmonary blastoma, pulmonary cyst, thyroid gland dysfunction (goiter, malignancy), sex cord stromal tumor, cystic nephroma, ciliary body medulloepithelioma, embryonal rhabdomyosarcoma, and tumors of the CNS, amongst others. Except for pituitary blastoma, which is an extremely rare tumor, none of the *DICER1*-associated neoplasms are pathognomonic for the syndrome. As such, detection of a germline pathogenic DICER1 variant in these neoplasms may be overlooked. We describe a case of bilateral SLCTs in a teenage girl subsequently found to carry a germline *DICER1* mutation.

Methods: Hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) were performed routinely per standard practice. Next generation sequencing (NGS) analyzed a peripheral blood specimen (Ambry Genetics).

Results: A 15-year-old female presented with hirsutism and secondary oligomenorrhea. Her workup showed an elevated testosterone level of 152.9 ng/dL (normal: 10-49 ng/dL), a 20 x 16 x 9 cm predominantly solid mass arising from the left ovary, a normal right ovary, and an enlarged thyroid with heterogenous enhancement and multiple nodules consistent with multinodular goiter.The left pelvic mass was then resected and a diagnosis of moderately differentiated SLCT was rendered. Six months later, laboratory and imaging studies showed elevated testosterone (147.2 ng/dL) and an 11.0 x 9.9 x 8.2 cm heterogeneously enhancing mass arising from the right ovary not seen in prior imaging studies. She subsequently underwent a right salpingoopherectomy, again consistent with a SLCT. Next generation sequencing revealed a pathogenic germline heterozygous mutation c.3856dupT, confirming the diagnosis of *DICER1* syndrome.

Conclusion: Including this patient, there are a total of just 8 reported cases of bilateral SLCTs with available *DICER1* status. Of these 8 cases, 7 were tested for germline *DICER1* mutations and all were positive (100%, 7/7). In comparison, only 53% (26/49) of patients with unilateral SLCTs harboring somatic *DICER1* mutations were also positive for germline mutations, a rate significantly lower than those with bilateral SLCTs ($p = 0.0338$, Fisher's exact test). Interestingly, mutation analysis on tumors from three of the patients with bilateral SLCT showed different somatic *DICER1* mutations harbored in each ovary, suggesting that these bilateral SLCTs should be regarded as primary and distinct SLCTs, not as a recurrence or metastasis. As such, bilateral SLCTs appear to occur exclusively in the setting of germline *DICER1* mutations and should be considered a pathognomonic feature of *DICER1* syndrome.

Pediatric Poster –Case Report
Virtual Poster Viewing

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Malignant Peritoneal Mesothelioma with EWSR1-ATF1 Gene Rearrangements in a 15 year-old Male

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****Resident Recruitment Award Presentation***

Background: Malignant peritoneal mesothelioma (MPM) is a neoplasm that shares similar genetic alterations with its pleural counterpart. Notably, *BAP1* inactivation/loss and *CDKN2A* and *NF2* deletion can be seen in a subset of pleural and peritoneal mesotheliomas. Recently, a small cohort of MPM with *EWSR1-ATF1* fusion and *BAP1* retention was reported in the literature. The youngest patient was a young adult (21 years of age). Here, we present a 15-year old patient with *EWSR1-ATF1* translocation-associated malignant peritoneal mesothelioma, whose tumor was also notable for diffuse TFE3 nuclear positivity.

Methods: The male patient presented at 15 years of age with a two-month history of constitutional symptoms, constipation, and suprapubic pain with urination. Abdominal ultrasound identified a 5 cm mass in the left lower quadrant that was localized to the mesentery by computerized tomography (CT) scan. An incisional biopsy was initially performed; however the patient developed small bowel obstruction and the affected mesentery with attached small bowel were resected. Final pathologic diagnosis was established in the resection specimen.

Results: The tumor consisted of sheets of epithelioid cells with ample eosinophilic or cleared cytoplasm. Focal alveolar and papillary growth patterns were present. Immunohistochemistry (IHC) was polyphenotypic, with the tumor expressing epithelial and mesenchymal markers (AE1/AE3, CAM5.1, EMA, p63 [scant nuclear], vimentin, and desmin [patchy]). CD99 were also strongly positive. TFE3 IHC, performed due to focal areas reminiscent of alveolar soft part sarcoma, showed diffuse nuclear positivity. Electron microscopy showed features consistent with an epithelial or mesothelial neoplasm. *EWSR1* breakapart FISH to rule out desmoplastic small round cell tumor (DSRCT) was positive for *EWSR1* gene rearrangement, but subsequent RNA sequencing identified the partner gene as *ATF1*, ruling out DSRCT. The clinical history, histology, and ancillary study findings supported the final diagnosis of MPM with *EWSR1-ATF1* gene rearrangements. Similar to other reported MPM with *EWSR1-ATF1* gene rearrangements, IHC for BAP1 was retained.

Conclusion: Pediatric mesenteric malignancies with predominantly epithelioid morphology have a large differential diagnosis based on location, frequency, and morphology. This case of MPM with *EWSR1-ATF1* gene rearrangements in a 15-year old patient illustrates the value of employing multiple techniques to narrow down the differential diagnosis and avoid diagnostic pitfalls that may be introduced by any single technique. In addition, the positive TFE3 IHC in this case of MPM could suggest a potential role of *TFE3* in mediating its oncogenesis, a role that has been demonstrated previously in laboratory model of clear cell sarcoma (a *EWSR1-ATF1* related neoplasm).

PediatricPoster – Case Report
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Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS): Early Discovery, Diagnosis, and Management in a Male Child.

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Background: Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS) is a recently described adenomatous polyposis coli (APC)-variant polyposis syndrome that results from mutations in the 1B promoter region of the APC gene. GAPPS follows an autosomal dominant inheritance pattern with variable penetrance that leads to carpeting of the gastric fundus by fundic gland polyps. Due to epigenetic phenomena, the GAPPS phenotype is characterized by polyposis of the proximal stomach only; the antrum and remainder of the gastrointestinal tract are spared. Similar to other syndromes in the APC family, GAPPS patients have an elevated risk of developing gastric dysplasia and subsequent progression to invasive adenocarcinoma. As a result, early identification and proper management of GAPPS patients is crucial in minimizing morbidity and mortality. Here we describe the diagnosis, pathologic findings, and management of GAPPS in a ten-year-old male which constitutes one of the earliest identified cases.

Methods: Our patient is a male child with no past medical history who originally presented at 8 years old with dysphagia. Endoscopy and biopsy results at that time were consistent with eosinophilic esophagitis. Routine surveillance endoscopy performed several months later revealed nodular mucosa in the gastric body and a normal antrum. Histopathological analysis of the nodules showed fundic gland polyps. Over the next year multiple additional endoscopies showed increasing nodularity within the gastric body, ultimately giving the appearance of “carpeting” with complete sparing of the antrum and proximal small bowel. At this point biopsy revealed fundic gland polyposis with multifocal low-grade dysplasia, and an extensive genetic workup for traditional polyposis syndromes was negative. Testing for the specific promoter 1B mutation of the APC gene was positive, confirming the diagnosis of GAPPS.

Results: With the diagnosis established, focus shifted towards appropriate clinical management. Given persistent multifocal low-grade dysplasia and the known increased risk for gastric adenocarcinoma in GAPPS, the patient was referred for prophylactic gastrectomy in lieu of continued surveillance. Grossly, the specimen showed extensive polyposis of the gastric body with sparing of the antrum and cardia. Exhaustive histopathologic evaluation revealed widespread low-grade dysplasia without high-grade dysplasia or invasive cancer.

Conclusion: Here we describe one of the youngest reported cases of GAPPS, including initial diagnosis, pathologic findings, and subsequent intervention. Our case illustrates the importance of early detection of the syndrome to allow for prophylactic intervention before the dysplasia-carcinoma sequence advances.

Pediatric Poster – Case Report
Virtual Poster Viewing

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Undifferentiated Round Cell Sarcoma with BCOR Internal Tandem Duplication: A Case with Predominant Rosetting Morphology

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Background: Next generation sequencing (NGS) continues to revise the classification of Ewing-like round cell sarcomas based on molecular alterations and phenotype-genotype correlations. Presently, Ewing-like sarcomas are sub-categorized into *CIC* rearranged*, BCOR* rearranged*,* and *EWSR1* and a non-ETS gene sarcomas*.* Recently, a subset found to harbor *BCOR* internal tandem duplications (ITD) has been identified in infants. *BCOR* ITD's have also been seen in clear cell sarcoma of kidney (CCSK), primitive myxoid mesenchymal tumor of infancy (PMMTI), and a subset of high grade neuroepithelial tumors (HGNET). We present a rare case of undifferentiated round cell sarcoma with *BCOR* ITD arising in infancy and highlight its unusual morphology.

Methods: A 4 week old female presents with a progressively enlarging soft tissue mass in the left temporal region. MRI shows a solid, 4.7 cm enhancing mass in the left temporal fossa without involvement of the underlying skull or intracranial extension. Biopsy and ancillary testing of the tumor confirmed the diagnosis of infantile soft tissue undifferentiated round cell sarcoma with abundant rosettes, *BCOR* ITD positive. Post chemotherapy the tumor had a significant decrease in size to 2.4 cm. Resection at 6 months of age demonstrated extensive treatment effect with no viable malignant cells, clear margins, and no evidence of metastatic disease.

Results: The tumor was composed almost entirely of sheets of rosettes of cells lacking a central lumen with hyperchromatic, vesicular nuclei, and inconspicuous nucleoli. There were rare areas of spindling with myxoid stroma and other focal areas of cells with clear cytoplasm. No prominent chicken-wire vasculature was identified. Conspicuous mitotic activity (up to 38/10 hpf) and areas of necrosis were present. Skeletal muscle was not involved. By immunohistochemistry the tumor was positive for BCOR, SATB2, TLE1, CD99 (diffuse cytoplasmic membranous) and was negative for cytokeratins, S100, myogenin, synaptophysin. Nuclear INI-1 staining was retained. NGS revealed a *BCOR* ITD of 66bp in exon 15.

Conclusion: Overlapping demographic and histologic features are now well recognized in undifferentiated round cell sarcomas, PMMTI and CCSK's with *BCOR* ITDs. Our case shows an unusual and striking rosette pattern with minimal myxoid areas. Although rosettes have been identified in these tumors, the notable diffuse rosette architecture present in this case appears quite rare. This case belongs to an emerging group of tumors with an undifferentiated round cell sarcoma phenotype that harbors *BCOR*-ITD or *YWHAE-NUTM2B*/*E* fusions that arise in infants. Our experience with this index case shows that strong *BCOR* positive IHC should prompt consideration of NGS capable of detecting ITDs over sarcoma fusion panels, especially in young infants.

Pediatric Poster – Case Report
Virtual Poster Viewing

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Periosteal Glomuvenous Malformation of a Hypoplastic Long Bone: A Case Report

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Background: Glomuvenous malformations (GVMs), formerly known as glomangiomas, are an uncommon sub-type of glomus tumors which present in childhood and are commonly confined to the skin and subcutaneous tissue. These perivascular mesenchymal neoplasms are primarily identified in the superficial subungual region, digits, palms, and in the precoccygeal soft tissue. Deep tissue glomuvenous malformations are uncommon. Here, we report an exceptional case of a symptomatic glomuvenous malformation abutting a hypoplastic distal femur.

Methods: An otherwise healthy 8-year-old girl presented with approximately two years of intermittent right leg pain and limited range of motion. On physical examination, a mass was palpable on the right lateral distal thigh, and a mild right leg length discrepancy was noted. The mass was radiographically occult on a plain radiograph without saucerization of the bone and a normal cortex. The mass was clinically stable three months after her initial presentation, at which time magnetic resonance imaging revealed a 2.8 x 0.8 x 0.8 cm benign-appearing periosteal mass. The patient underwent excision of the lesion by the orthopedic oncological surgery service. Intraoperatively, the lesion appeared intimate with the periosteum, but free from the femoral bone. The lesion was circumferentially dissected from the surrounding tissues and removed in an en bloc fashion.

Results: The specimen was a single fragment of tan-pink and tan-yellow soft tissue, measuring 2.4 x 2.0 x 1.1 cm. It was plaque-like with a smooth periosteal surface, an opposite irregular surface, and a tan-pink, nodular cut surface. Microscopy showed a poorly circumscribed lesion consisting of gaping vascular channels lined by normal-appearing endothelial cells. These vascular channels were closely surrounded by cytologically benign glomus cells with round nuclei and eosinophilic cytoplasm. Mitotic activity was inconspicuous. The tumor cells were immunoreactive for Caldesmon. Fluorescence in-situ hybridization studies were negative for EWSR1, FUS, and SS18 rearrangements. These features define a glomuvenous malformation. Following the surgery, the patient had significant improvement of her symptoms. One year after her surgery, she has remained asymptomatic with normal range of motion, symmetric leg lengths, and unremarkable follow up magnetic resonance imaging.

Conclusion: We have found only three case reports of periosteal glomuvenous malformations of long bones in the literature, none of which had an associated limb hypoplasia. We present the first case of a periosteal glomuvenous malformation of a long bone that is associated with leg-length discrepancy.

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Delayed Diagnosis of Intraarticular Synovial Sarcoma of the Left Knee: A Case Report and Literature Review

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Background: Intraarticular tumors are rare and most of them are benign types, such as synovial lipomatosis, synovial osteochondromatosis, pigmented villonodular synovitis and synovial hemangiomas. Synovial sarcoma arising within a joint is extremely rare, with less than 50 cases reported in the literature. The most common location is the knee. Its rarity and nonspecific radiological features pose a diagnostic challenge. The present case report describes a case of intraarticular synovial sarcoma with a delayed diagnosis.

Methods: Patient information was gathered from electrical medical record. Routine and immunohistochemical stains, FISH with SS18 (18q11.2) dual color break-apart probe and OncoKids® NGS panel were performed on the excisional specimen. The authors also performed a literature search using the PubMed search engine with the following search terms: intraarticular, synovial sarcoma and knee.

Results: A 17-year-old male presented with left knee pain for 9 years and postoperative (arthroscopic surgery repair of discoid meniscus) stiffness for about 7 years. He received arthroscopic lysis of adhesions, aggressive physical therapy and guided growth procedure with hardware placement without significant improvement. Left knee biopsy was performed about 4 years ago, which was diagnosed as focal nodular synovitis outside. Recent MRI and x-rays of the left knee appeared to show an osteophyte formation of the distal pole of the patella as well as possibly degenerative change or a cystic lesion around the anterior lateral proximal tibia. The patient underwent left knee arthrotomy with an extensive lysis of adhesions and arthrofibrosis excision. Histological examination of excision revealed variably cellular proliferation composed of spindle cells admixed with lymphoplasmacytic infiltrates. The spindle cells were strongly and diffusely positive for TLE1 and CD99, patchy positive for AE1/AE3 and EMA, negative for S100, SATB2 and CD45. FISH showed that 60% of cell population harbored a SS18 gene region rearrangement. OncoKids® NGS panel showed SS18- SSX1 fusion, confirming the diagnosis of intraarticular synovial sarcoma, monophasic. The patient received neoadjuvant chemotherapy and radiation and was alive with disease ten months after diagnosis. Literature review shows that intraarticular synovial sarcoma can lead to long delays in diagnosis.

Conclusion: Intraarticular synovial sarcoma should be considered as a potential diagnosis in patients with unexplained long-standing knee pain and or stiffness.

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Anaplastic Sarcoma of the Kidney

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Background: Anaplastic sarcoma of the kidney (ASK) is a rare renal tumor. First described in 2007, to date less than thirty of these tumors have been reported in the literature. ASK is primarily a histologic diagnosis, consisting of spindle cells in a fascicular pattern with prominent anaplastic nuclear changes and brisk mitoses. Areas of chondroid or rhabdomyocytic differentiation are common, along with multiple multiloculated cysts lined by hobnail epithelium. Recent literature has identified DICER1 mutations within a cohort of ASK, suggesting that this entity belongs within the category of DICER1 syndrome tumors.

Methods: A twenty-month-old female presented with a four-day history of hematuria. Radiological studies revealed a left renal mass with mixed solid and cystic features located in the superior pole. She underwent a left total nephroureterectomy. Grossly, the tumor measured 7.3 x 6.8 x 6.8 cm and weighed 285 grams, arose from within the superior pole of the renal parenchyma, and was well-encapsulated. The tumor had many loculated cavities admixed with solid pink-yellow fleshy areas and few pinpoint foci of necrosis.

Results: Histologically, the tumor was comprised of short, intersecting fascicles of spindle cells and small, cystically dilated, entrapped tubules. The neoplastic cells were plump with inconspicuous nucleoli showing marked pleomorphism and anaplasia. Brisk mitotic activity with atypical multipolar forms were present. The cystic component showed dilated tubules with hobnail epithelium reminiscent of cystic nephroma. Scattered throughout the tumor were islands of differentiating neuroblastic cells with neurofibrillary background and ganglion cell morphology. Focal areas of myxoid background were also present.
Immunohistochemical staining revealed the neoplastic spindle cells to be positive for vimentin, Bcl-2, p53, and CD99, with variable cyclin-D1 positivity. WT1, PAX8, desmin, and myogenin were negative. The areas of ganglionic differentiation were positive for S100 and NSE. INI1 expression was retained. Chromosomal cytogenomic microarray showed a loss of 35.1 Mb at 10p15.3p11.21. Genomic sequencing revealed somatic mutations of BRAFpV600E, PPMIDp.K480, p.T483fs, p.E525, p.N505fs, and DICER1pE1813K and a germline mutation of DICER1p.A581fs.

Conclusion: The histological findings and pattern of immunohistochemistry supported a diagnosis of ASK. The tumor also displayed ganglionic differentiation, which has not been previously described in the literature. Although no chromosomal abnormalities were identified, microarray revealed that our patient had both a somatic and germline DICER1 mutation, along with aberrant TP53 staining, consistent with recent research.

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Post-transplant Lymphoproliferative Disorder (PTLD) of Burkitt Lymphoma Type Relapsing as Classic Hodgkin Lymphoma; An Unusual Pediatric Case

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Background: PTLD represents a potentially life-threatening complication after solid organ transplantation. There are four types of PTLD including non-destructive (formerly "early lesions"), polymorphic, monomorphic, and classic Hodgkin lymphoma types, among which monomorphic Burkitt lymphoma type is uncommon and classic Hodgkin lymphoma is very rare. We present an unusual pediatric case initially presenting as Burkitt lymphoma but later relapsing as classic Hodgkin lymphoma.

Methods: An eight-year-old male underwent cardiac transplant at 5 weeks of age for congenital heart disease. At age 1, he developed tonsillar follicular lymphoid hyperplasia and diagnosed with early PTLD. At age 3, he developed pulmonary monomorphic Burkitt lymphoma-type PTLD (*MYC* rearrangement positive) for which he received chemotherapy for 3 months and achieved remission. At age 8, he presented with fever, cough and chest pain. Chest CT revealed multiple pulmonary consolidations and hilar lymphadenopathy, suspicious for Burkitt lymphoma relapse. Surprisingly, ultrasound-guided biopsy of the lung nodule revealed a heterogeneous lymphoid infiltrate with a few interspersed large atypical cells that expressed CD15, PAX5 and CD30, but were negative for CD20, CD3, and ALK-1. In situ hybridization for EBV was positive in the large cells. The overall findings were consistent with classic Hodgkin lymphoma PTLD.

Results: The patient is on chemotherapy and alive currently. Our case is unique because it relapsed after multiple years of treatment from Burkitt lymphoma to an entirely separate entity, classic Hodgkin lymphoma, which is an extremely rare finding in this age group.

Conclusion: Burkitt lymphoma relapse as classic Hodgkin lymphoma has not been reported in pediatric patients. It is important to realize its existence thus to facilitate the diagnostic process and appropriate clinical management.

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"EPIC" Nasal Polyps: Epstein-Barr Virus-positive Plasmacytomas in a 17-year-old ImmunoCompetent Patient

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Background: Plasmacytomas are monoclonal plasma cell neoplasms forming masses. Some reports have shown EBV positivity in plasmacytomas in immunocompetent patients (EPIC=EBV-positive plasmacytoma in immunocompetent patient). EPIC has been described only in adults. We report an extramedullary plasmacytoma presenting as two separate polypoid masses in the nasal cavity of an immunocompetent 17 yo boy.

Methods: The patient presented due to an oropharyngeal mass present for a month. MRI revealed 2 distinct pedunculated nasal cavity masses. The patient underwent surgical resection: an 8.5 cm mass was removed from the right and a 1.5 cm mass from the left.

Results: A dense, mostly mature plasma cell infiltrate was present with variable degrees of anaplasia and plasmablastic features (Figure 1). Notably, the left infiltrate showed predominantly plasmablastic morphology (Figure 2). The neoplastic cells were strongly positive for CD138, IgG, and MUM-1, with aberrant CD4, CD56, and CD117 expression in a subset (Figure 3). The cells were kappa-restricted and strongly positive for EBER (Figure 4). Ki-67 index was <30%. ALK, HHV8, CD30, CD20, EMA, IgA, IgM, and IgG4 immunostains were negative. FISH using a myeloma targeted panel showed gains of 1q21.3 (CKS1B), 3q27 (BCL6), and 11q23 (KMT2A); there was no evidence of ALK rearrangement. A small lymphocytic infiltrate involved both masses (Figure 6), which flow cytometry and T cell receptor gene rearrangement studies revealed as an oligoclonal, CD8 and CD57 positive cytotoxic T cell population; this same T cell population was also detected at a low frequency (5% of total white blood cells) in the peripheral blood. Bone marrow biopsy demonstrated polytypic plasma cells comprising less than 0.1% of marrow cellularity. Additional studies to assess renal function, immune function, and infectious disease status, including HIV and EBV titer, were all within normal limits.

Conclusion: Although EPIC has been previously described, it has not yet been reported in a pediatric patient. Additionally, this specific hyperdiploid cytogenetic abnormality has yet to be reported. Although focal plasmablastic morphology may be seen in EPIC, we observed distinctive morphology between the right and left plasmacytomas. The clinical significance of this finding is unclear, however may provide insight into pathogenesis of this lesion or may be a unique morphologic feature of EPIC in pediatric patients, i.e., more prominent plasmablastic morphology as compared to adult cases. Recognition of EPIC is important to avoid misdiagnosis of plasmablastic lymphoma, which requires very different treatment than plasmacytoma. Additionally, diagnosis of EPIC should prompt complete workup with laboratory and imaging studies to assess for plasma cell myeloma or other sites of involvement.

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Primary Renal Myoepithelial Carcinoma with EWSR1-KLF15 Fusion: A Third Reported Case

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Background: Myoepithelial tumors, including myoepithelial carcinoma, have been increasingly recognized at sites beyond the salivary glands but remain rare tumors, particularly at visceral sites. Two primary renal myoepithelial carcinomas were identified in a retrospective COG study of pediatric renal carcinomas, both of which exhibited an EWSR1-KLF15 fusion (Cajaiba et al. Am J Surg Pathol 2016;40:386-394). We report a 6-year-old boy with hematuria and a large left kidney mass, which proved to be a third example of myoepithelial carcinoma with EWSR1-KLF15 fusion.

Methods: Standard gross and microscopic examination were performed on the resected tissue. Immunohistochemical staining (IHC) was performed on select slides with appropriately reactive controls. Karyotyping was performed on cultured cells from fresh tumor tissue. Total RNA was isolated from a formalin-fixed paraffin-embedded block and anchored-multiplex fusion testing targeting 93 genes including EWSR1 (Custom FusionPlex Kit, Archer Dx) was performed by massively parallel sequencing (Illumina MiSeq).

Results: The radical nephrectomy specimen contained a 7.9 cm, well circumscribed, lobulated, heterogeneous tumor at the lower pole. There were solid, nested, reticular, trabecular and pseudopapillary architectural patterns, with frequent myxoid and hyaline stroma. Tumor cells were epithelioid, plasmacytoid, clear, or slightly spindled, with brisk mitotic activity and focal necrosis. Cytologic atypia was focally prominent. The tumor was unencapsulated and infiltrative, including renal sinus invasion. Two of five para-aortic lymph nodes harbored metastatic disease. IHC was diffusely positive for vimentin, cyclin-D1 and SATB2, and focally positive for cytokeratin AE1/AE3, S100 protein, SOX-10, CD10, PAX8, and TFE3. INI-1 was retained. Other stains including p63, EMA, CK7, SMA, calponin, WT1, CD117, melan-A, HMB-45 and synaptophysin were negative. Sequencing identified an EWSR1-KLF15 fusion transcript. Conventional cytogenetics showed an unbalanced t(3;22)(q21;q12) translocation, which corresponds to the fusion.

Conclusion: This case of myoepithelial carcinoma with EWSR1-KLF15 fusion bears a strong resemblance to the two cases previously reported in a retrospective study by COG, and it might represent the first prospective diagnosis of this entity. All three tumors show varied morphology in terms of architecture and cytology and they are accompanied by myxoid or hyaline stromal alterations, while IHC is consistent with myoepithelial differentiation. In the setting of a renal neoplasm with varied morphology, consideration of myoepithelial carcinoma and ultimately recognition of an EWSR1 rearrangement, or more specifically the EWSR1-KLF15 fusion or its corresponding t(3;22) translocation, may help to firmly establish the diagnosis.

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Dermatofibrosarcoma Protuberans of the Breast with Pseudoangiomatous Spaces: Giant Cell Fibroblastoma or Pseudoangiomatous Stromal Hyperplasia?

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Background: Dermatofibrosarcoma protuberans (DSFP) is a dermal-based spindle-cell neoplasm. Pediatric cases typically show a genetic rearrangement of the PDGFB gene (22q13.1) with the COL1A1 gene. DFSP shares this rearrangement with the related entity of giant cell fibroblastoma, a low cellularity neoplasm of giant cells and spindle cells, often forming pseudoangiomatous spaces, which can exist along with DFSP. Pseudoangiomatous spaces also characterize pseudoangiomatous stromal hyperplasia of breast tissue (PASH). A 13-year-old male presented with DFSP of the left breast with histologic features of gynecomastia and pseudoangiomatous spaces in adjacent tissue. We sought to distinguish pseudoangiomatous spaces of giant cell fibroblastoma/DFSP from PASH in this setting.

Methods: Standard gross and microscopic examination were performed on the resected tissue. Immunohistochemical staining (IHC) was performed on select slides with appropriately reactive controls. Multiplex morphometric florescent in situ hybridization (FISH) with a DNA probe set for each end of the PDGFB gene (CytoTest, Inc.) was utilized to assess for a PDGFB gene rearrangement.

Results: The resected breast tissue included a 3.2 cm homogeneous, firm, well-circumscribed dermal mass and an adjacent 4.2 cm area of fibrous tissue. H&E sections of the mass revealed a cellular proliferation of plump, eosinophilic, spindle cells with punctate to vesicular chromatin arranged in a storiform pattern. IHC showed these cells to be positive for CD34 (diffuse) and SMA (patchy) but negative for S100 protein. Beta-catenin showed only cytoplasmic staining (negative for nuclear localization), and H3K27me nuclear staining was retained. FISH for a PDGFB gene rearrangement in the DFSP-like area was positive in 181/200 nuclei (90.5%). The fibrous area lacked giant cells but contained pseudoangiomatous spaces lined by bland, stellate cells. IHC on this area showed the cells to be CD34 positive but negative for CD31, SMA, and Fli-1. FISH detected no rearrangement of the PDGFB gene (0/200 nuclei). We concluded that the pseudoangiomatous spaces represented PASH and not a giant-cell-fibroblastoma-like extension of the DFSP.

Conclusion: PASH is a benign breast lesion that was first described in adults, but it is increasingly recognized in the pediatric population and can be associated with gynecomastia. The pseudoangiomatous spaces of this entity can appear similar to giant cell fibroblastoma and in a context such as this case could be mistaken for a continuum of the DFSP, with implications for adequacy of resection. Also, since both PASH and DSFP tend to recur, FISH analysis might be helpful in differentiating a recurrent mass lesion.

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An Unexpected Case of Neonatal Acute Lymphoblastic Leukemia

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Background: Neonatal leukemia is a rare form of leukemia which occurs within the first 4 weeks of life; it accounts for <1% of childhood leukemias. Two-thirds are acute myeloid leukemia, while the remaining third are acute lymphoblastic leukemia (ALL), predominantly of B-lineage. *KMT2A* rearrangements are present in 91% of leukemias diagnosed at less than 6 months of age. In this case report, we present an unexpected B-ALL identified by forensic autopsy in a 7-week-old female infant.

Methods: A forensic autopsy was requested during investigation of an unexpected infant death. Pertinent history included term birth following uncomplicated pregnancy and delivery. All neonatal screening was normal; neonatal checkups were notable for weights at the 20th and 5th percentiles, at day 2 and day 11 respectively. She was reportedly feeding well until the day of death when she became inconsolable with progressive abdominal distention. During transport to the hospital, she had a witnessed cardiopulmonary arrest; resuscitation efforts were unsuccessful.

Results: At autopsy, she was dehydrated with extreme cutaneous pallor and subcutaneous and gastric mucosal petechiae. Growth parameters were well below expected for age. Organomegaly was dramatic, notably of pancreas, liver, and spleen. Histologic examination demonstrated systemic involvement by a population of small hematopoietic blast-like cells occluding vessels and expanding parenchyma throughout all organs. By immunohistochemistry, the cells expressed CD45, CD43, CD79a and Pax5. A paucity of red blood cells was noted, especially in the spleen. Interphase fluorescent in-situ hybridization demonstrated a *KMT2A* gene rearrangement, and excluded the three most common B-ALL fusion partners (*AFF1, MLLT1,* and *MLLT3*). These findings were consistent with B-ALL.

Conclusion: Although 7 weeks old at the time of her demise, the extent and severity of the decedent's disease was suggestive of a neonatal/congenital onset. Neonatal leukemias commonly present with hepatosplenomegaly and skin lesions. Overall survival is poor, particularly in those with *KMT2A* rearrangements, a white blood count of >300 K/µL on presentation, and onset at less than 6 months of age. Extreme hyperleukocytosis at presentation results in anemia, respiratory distress with hypoxia, and end-organ damage. Physical occlusion of vessels can induce thrombotic events.
Sudden unexpected infant deaths are not uncommon in the coroner/medical examiner field; some of the most difficult cases are those without answers. This report highlights the intersection of multiple disciplines in pathology, the need for awareness of this entity in the forensic community, and how collaborative efforts to arrive at a definitive diagnosis in this case provided closure to the family.

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Infantile Hemangioma Arising Within a Mediastinal Mature Cystic Teratoma in a Teenaged Girl

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Background: It is rare for mediastinal germ cell tumors to harbor secondary neoplasms. Here, we report the first case of a phenotypically characteristic infantile hemangioma within a mediastinal mature cystic teratoma.

Methods: A 19-year-old, never pregnant, female presented with one month of coughing, sore throat, and right anterior chest and back pain. A chest computed tomography (CT) imaging study showed a heterogenous, cystic mass in the right lower anterior mediastinum, measuring 5.9 x 6.0 x 6.4 cm. She underwent a resection of the mediastinal mass with a portion of lung right lower lobe, thymus, and pericardium. The patient had an unremarkable post-operative course. Follow-up CT imaging six months after discharge demonstrated no intrathoracic metastasis or recurrence.

Results: The circumscribed lesion measured 6.3 x 6.0 x 3.8 cm and consisted of two components: a tan-white firm outer shell with a thickness range of 0.6-1.2 cm, and an inner tan-yellow soft tissue component, measuring 4.8 cm in diameter. There were abundant tan-yellow calcified areas and blond hair present within the lesion. Microscopically, the lesion was predominantly composed of mature, somatic tissue with squamous-lined cysts. A hypercellular area, measuring 1.1 cm in greatest dimension, containing plump endothelial cells and pericytes with clear cytoplasm was identified adjacent to intestinal-type epithelial elements. The endothelial cells and pericytes formed small capillaries with inconspicuous lumens. Mitotic figures were evident. Immunohistochemistry studies showed expression of GLUT-1, CD31, and ERG. There were no neural elements, immature components, or malignant elements in the specimen. Together, these findings were diagnostic of a mature cystic mediastinal teratoma harboring an infantile hemangioma.

Conclusion: We report the first case of a mediastinal mature cystic teratoma harboring an infantile hemangioma. The etiology of infantile hemangiomas is unclear. A well-liked theory proposes that infantile hemangiomas arise from the embolization of placental chorionic villus mesenchymal cells into the fetus during gestation. Our case argues against this theory as mediastinal teratomas are thought to derive from ectopic primordial germ cells. It is unlikely that this component of the patient's teratoma had an occult embolic origin from her placenta that was undetected for nineteen years. It is also unlikely that the vascular lesion originated from unsampled placental tissue within the teratoma as trophoblastic tissue is derived from the embryo's outer cell mass while mature teratomas recapitulate tissues derived only from the inner cell mass. We postulate that the infantile hemangioma component may have arisen from germ cell derived placental type angioblasts that could have developed without associated trophoblast.

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Immature Extragonadal Teratoma in an Infant: A Case Report

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Background: Extragonadal teratomas are rare tumors comprised of cells from all three germ cell layers. They are more common in neonates under 6 months old and most commonly arise in the sacrococcygeal region. In children older than 6 months, extragonadal teratomas are even rarer and are typically more aggressive. An exclusively abdominal or retroperitoneal location is uncommon.

Methods: Our patient is a 9-month-old male who was found to have an abdominal mass on a routine well child visit. Laboratory results revealed a slightly increased AFP of 347 ng/mL. Imaging studies showed an encapsulated, mixed solid and cystic mass measuring 15.7 x 13.6 x 10.4 cm that was possibly arising from the left lobe of the liver. Areas of necrosis, septations, and calcification were identified. The differential diagnosis included mesenchymal hamartoma, hepatoblastoma and sarcoma. He was taken to the OR for surgical resection. During surgery, it was discovered that the tumor was focally arising from the anterior stomach, without hepatic involvement.

Results: Upon gross examination, the mass was well encapsulated. The cut surface was tan-white with solid and cystic areas. The cystic areas contained clear fluid. Internal septations and areas of calcification were also present. Histologically, the mass was composed almost entirely of mature fetal tissues of ectodermal, mesodermal and endodermal origins, consistent with a teratoma. Two small distinct foci of immature neuroepithelium were identified, qualifying this as a grade 2 immature teratoma. Interestingly, although the AFP level was elevated, no yolk sac tumor was identified.

Conclusion: We present a case of a rare immature extragonadal teratoma arising from the stomach. Immature teratomas of the adult ovary are considered malignant, but this is not the case in pediatric teratomas. However, extragonadal immature teratomas are associated with an increased risk of recurrence and future development of a yolk sac tumor. The clinical stage of these tumors, as well as the completeness of surgical resection, are the most important prognostic factors to consider. A thorough histologic examination should be performed in all cases to evaluate for the presence of immaturity and yolk sac components.

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Congenital Pleuropulmonary Blastoma with Rapid Progression from Type 1 to Type 2

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Background: Congenital cystic adenomatoid malformation (CCAM) is a lung abnormality characterized radiologically by a cystic mass, often with associated bronchial atresia/mucocele, thought to be distinct from the DICER1-associated tumor pleuropulmonary blastoma (PPB). Old reports of PPB or rhabdomyosarcoma "arising in CCAM" are generally now thought to reflect solid PPB components in an otherwise cystic PPB. For radiologically suspected CCAM, there is debate about whether to watch and wait given the risk of pleuropulmonary blastoma (PPB), a bland cystic (type 1) or variably solid (types 2 and 3) malignant tumor of lung/pleura. Watch and wait proponents cite the relative infrequency of PPB compared to CCAM as well as the low morbidity and mortality of type 1 PPB.

Methods: We studied clinical, radiologic, and pathologic features of an infant girl with a cystic lung mass that rapidly developed a sizeable solid component.

Results: Antenatal ultrasound at 36 weeks revealed cystic lung suggestive of CCAM. Postnatal radiographs showed a multiloculated right lower lobe mass with mediastinal shift. At age 1 month, chest radiograph demonstrated interval increase in the size of the multiloculated cystic mass. At age 3 months, CT revealed a 3.0-cm solid component within a predominantly cystic 8-cm mass, raising suspicion for PPB. At age 4 months, a right lower lobectomy was performed. Grossly, there was a 2.4-cm solid component within a 9.5-cm mass. Microscopic examination revealed type 2 PPB. Cystic regions showed areas with subepithelial coalescence of bland round to spindled mesenchymal cells. Solid regions demonstrated primitive spindled cells with sparse myogenic differentiation, confirmed by desmin and myogenin stains. Away from the tumor, lung showed maldevelopment resembling that of CCAM, with enlarged airspaces and excess thin-walled airway-like structures. *DICER1* testing showed the variant c.5479delC (p.Leu1827Trpfs*11) in the patient and her father. The patient had an additional variant, c.1168T>C. At last follow-up (age 3 years), she was recovering well following resection of a stage pT1a poorly differentiated Sertoli-Leydig cell tumor of the ovary; she had no evidence of residual/recurrent PPB.

Conclusion: The findings illustrate the potential for an infant to develop a solid component in a radiologically fully cystic congenital lesion, highlighting the potential for rapid growth in congenital PPB. This is an important consideration in establishing guidelines for interval imaging of congenital cystic lung disease. Additionally, it suggests that congenital PPB may be associated with CCAM-like changes, perhaps because of impingement by tumor on developing airways supplying the affected lung tissue; this expands understanding of a potential relationship between PPB and CCAM.

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Primary Angiosarcoma of the Ovary: Case Report of a Rare Malignant Paediatric Tumour

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Background: Primary ovarian angiosarcomas are rare and aggressive vascular tumours with very limited number of paediatric cases reported in the literature. These tumours sometimes arise in association with teratomas.

Methods: We report a case of ovarian angiosarcoma in a 16-year-old girl with no significant past medical history or relevant family history. She presented with abdominal pain and underwent salpingo-oophorectomy with a clinical suspicion of torted ovarian cyst.

Results: Macroscopically, there was a haemorrhagic and focally necrotic solid mass 85mm x 75mm x 65 mm replacing the entire ovary. Histologically, the tumour showed diffuse proliferation of markedly atypical spindle cells, which in places were forming vascular spaces. There was invasion into surrounding soft tissue. The pattern of immunohistochemical stains were those of angiosarcoma. No teratomatous component was identified despite extensive sampling of the tumour. The patient received chemotherapy and radiotherapy. The clinical course was complicated by multiple metastases including to the appendix, lung and pleural surfaces, requiring operations and surgical excisions. The patient died 6 months after the initial diagnosis.

Conclusion: Ovarian angiosarcomas generally have a poor prognosis with a 5-year-survival rate of less than 30%, if non-metastatic. Almost all of the cases with metastasis die within the first 12 months from diagnosis. Awareness of occurrence of this entity can help with an accurate and timely diagnosis in dealing with unusual paediatric ovarian tumours.

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An Unusual Presentation of a Hepatoblastoma in an 11-year-old Girl

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Background: Hepatoblastoma (HB) is a rare malignancy, usually presenting in children younger than 5 years. We present a case with an atypical presentation and discuss the differential diagnoses.

Methods: An 11-year-old girl with Klippel-Feil syndrome presented with a liver mass. Liver USS and MRI showed a 76mm lesion in the right lobe. Serum AFP was raised at 390kIU/L (normal <11). Whole body CT/PET scans showed a non-FDG avid primary lesion with no other lesions. The liver biopsy showed sheets of well differentiated hepatocytes with a vague mosaic dark and light pattern and widened cell plates. There were no crowded or small cell areas and there was no extramedullary haematopoiesis. The histological differential diagnoses included benign and malignant epithelial hepatic tumours. Glutamine synthetase (GS) showed diffuse cytoplasmic staining and glypican-3 (GPC) was finely granular. The biopsy was reported as a malignant hepatocellular neoplasm, favouring a well differentiated fetal HB with low mitotic activity. A right hemi-hepatectomy showed a multinodular, unencapsulated, variegated 70mm mass. Most nodules had similar histological features to the biopsy whilst other nodules had a crowded appearance with increased mitotic activity (33/10HPF), but without anaplastic, small cell or mesenchymal components. GPC showed finely granular staining in the well-differentiated component and coarse granular staining in the mitotically active component; GS was strong and diffuse; HepPar showed faint granular cytoplasmic staining. The final diagnosis was HB, epithelial type, predominantly well-differentiated fetal pattern, with areas of crowded, mitotically active fetal pattern, COG stage II. She did not receive further treatment and is well, without recurrence 3 years following surgery.

Results: Liver tumours are uncommon in this age group, usually sporadic but can be associated with familial syndromes. The association of HB with Klippel-Feil syndrome is not reported. HB arises mostly in boys within the first 3 years of life. Only 14 cases of HB in patients older than 5 years have been published, of which 4 were in girls. Patients typically present with markedly elevated AFP (>1000kIU/L), however it was only mildly elevated here. Other neoplasms in this age group include focal nodular hyperplasia, vascular tumours, hepatic adenoma or carcinoma.

Conclusion: There is a low incidence of HB beyond early childhood in females and its biological behaviour in this cohort is not well studied. Pathologists should be cognisant of this atypical presentation and consider this differential diagnosis even in older children, with well differentiated hepatocellular masses and a mildly raised AFP.

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Primary Spindle Cell Rhabdomyosarcoma of Bone with a Novel MYOD1 Mutation

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Background: Rhabdomyosarcomas are the most common soft tissue sarcoma in children. Spindle cell/sclerosing RMS is a rare subtype, encompassing poor prognosis tumors with *MYOD1* mutations, better prognosis tumors with *VGLL2/NCOA2* fusions, and a subgroup lacking recurrent genetic aberrations. *MYOD1* mutated RMS typically carry an exon 1 pL122R mutation. RMS arising in bone is extremely rare but has been recently reported in cases with *TFCP2* fusions. These tumors have a hybrid spindle cell and epithelioid morphology, a predilection for craniofacial bones, and display aggressive behavior. We report here a primary spindle cell/sclerosing rhabdomyosarcoma of bone with a novel *MYOD1* mutation in a child.

Methods: The patient's information was gathered from the electronic medical record and prior pathology records. Routine and immunohistochemical (IHC) stains and next generation sequencing (NGS) panel were performed on the primary excision and recurrence specimens.

Results: A 13 year old male underwent left mandible resection for recurrent tumor. The first biopsy from 3 years prior showed an unclassifiable high-grade spindle cell lesion lacking osteoid that was BCOR and SATB2 positive and desmin negative by IHC. The primary resection specimen contained osteoid-like material and was diagnosed as high-grade osteosarcoma, fibrosarcomatous type. Molecular studies were negative for clinically significant RNA fusions and no mutations in the *MYOD1* gene. Despite chemotherapy the tumor recurred 3 years later. The current resection showed mixed histologic features of spindled, sclerosing and round cell areas containing "strap cells" without osteoid, which raised the possibility of a myogenic component. IHC demonstrated nuclear MyoD1 and cytoplasmic desmin and ALK positivity, findings consistent with spindle cell rhabdomyosarcoma of bone. An additional biopsy revealed focal myogenin nuclear positivity. Molecular diagnostic results from the current resection showed an unusual *MYOD1* p.Phe129HisfsTer80 frameshift variant that was not identified on previous cases.

Conclusion: To our knowledge this is the youngest patient reported to have a primary spindle cell rhabdomyosarcoma of bone. This case matches well with previous descriptions of this rare tumor, with comparable histologic and immunohistochemical features (MyoD1, desmin and ALK positivity, with limited expression of myogenin). The finding of a *MYOD1* mutation is consistent with the IHC, but with the intriguing finding of a novel frameshift mutation that differs from the canonical pL122R mutation. The lack of rhabdomyosarcoma-like areas and a *MYOD1* mutation in the original biopsy is puzzling, raising the possibility of either a second malignancy or treatment-related transformation. RNA sequencing to investigate for a *TFCP2* fusion is currently in progress.

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Bilateral Nephroblastic Tumors and a Complex Renal Vascular Anomaly in a Patient with a Somatic Mosaic RASopathy: Novel Histopathologic Features and Molecular Insights

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****Resident Recruitment Award Presentation***

Background: Mosaic RASopathies are an emerging group of disorders that are characterized by mosaic or post-zygotic activation mutations in genes of the RAS/MAPKinase pathway, including *KRAS*, *NRAS*, and *HRAS*. A wide variety of phenotypes occur, ranging from limited, localized forms to syndromic cases with multi-system involvement. The mutational spectrum differs from germline RASopathies, with cancer-associated mutations being more common. Rare cases with pediatric malignancies have been documented; although the lifetime cancer risk and underlying molecular mechanisms remain largely unknown. We report renal pathological and molecular findings in 22-month-old boy with a somatic oncogenic *KRAS* p.G12D variant and a syndromic presentation (including a unilateral epidermal nevus, ipsilateral lower limb overgrowth and bilateral nephroblastic renal tumors) that overlapped with CLOVES and other *PIK3CA*-related overgrowth syndromes (PROS). Right nephrectomy and left nephron sparing surgery was performed after neoadjuvant chemotherapy.

Methods: Pathological findings were reviewed and representative tissue areas identified for molecular genetic testing with the Oncomine Childhood Cancer Research Assay (Thermo Fisher Scientific). Tissue cores were obtained from FFPE blocks for isolation of DNA and RNA according to manufacturer's protocol.

Results: Pathological examination showed multiple discrete encapsulated nodules of well-differentiated nephrogenic epithelium consistent with epithelial Wilms tumors (WT) in both kidneys, in addition to multiple perilobular and adenomatous nephrogenic rests (NRs). The resected right kidney and perirenal fat were diffusely involved by a complex vascular anomaly with large thick-walled veins, with focal intramural capillary proliferations, myxoid change, chronic inflammation, and involvement of nerves. Molecular testing identified a mosaic *KRAS* p.G12D variant at high allele frequency (~40-60%) in bilateral NRs and WTs, and in the unilateral vascular anomaly, but only at 3-4% in the normal left kidney. In addition, two right-sided WTs harbored a *FBXW7* p.R479G cancer hotspot variant in virtually all cells (40-44%) that was not seen in the associated NRs.

Conclusion: We document the first case of a somatic RASopathy with bilateral nephrogenic tumors (NR and WT), and in addition describe a novel complex FAVA-like renal vascular anomaly. Virtually all affected cells harbored a somatic *KRAS* p.G12D variant, whereas a significantly lower level of mosaicism was found in the normal kidney. The occurrence of a secondary somatic cancer hotspot mutation (*FBXW7* p.R479G) in the WT but not the associated NR suggests that Wilms tumorigenesis in somatic overgrowth disorders may involve additional driver mutations.

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Neuropathological Findings in a Wieacker-Wolff Syndrome with ZC4H2 Mutation

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Background: Wieacker-Wolff syndrome (WWS), an X-linked syndrome, is a rare disease with clinical manifestations of congenital contracture of feet, progressive neurologic muscle atrophy, and intellectual disability. Recently, mutations within the ZC4H2 gene have been linked with the Wieacker-Wolff phenotype and the occurrence of arthrogryposis multiplex congenita (AMC). The underlying mechanism for the contracture is unknown but was thought most likely neurogenic from animal model studies. This represents the first known case of WWS to undergo postmortem examination and pathological evaluation of the central nervous system.

Methods: We describe the neuropathological findings in a 4 month old, ex-31 week twin male neonate transferred to our hospital for further workup and genetic evaluation of AMC. Significant prenatal history included twin pregnancy, intrauterine growth restriction and maternal connective tissue disease. During the admission, the patient had respiratory failure requiring mechanical ventilation, multiple respiratory infections, and seizures. Clinical exome sequencing identified a novel variant in *ZC4H2* (c.505T>C) of uncertain significance but was deemed to be more likely disease-causing. Patient underwent compassionate extubation. Postmortem examination was performed.

Results: The general autopsy findings were consistent with the clinical diagnosis of WWS (AMC and dysmorphic facial features). Formal neuropathology examination revealed a small brain with mild flattening of bilateral parietal lobes. There was significant white matter loss with thin corpus callosum and dilatation of lateral ventricles. Transverse sections of the spinal cord were small. Histological examination revealed hypomyelination of the white matter and diffuse white matter gliosis. The corticospinal tracts in the brainstem and the spinal cord were thin and gliotic. The spinal cord anterior horn cells demonstrated no dysgenesis and only mild loss. The periventricular, cerebellar and spinal cord white matter showed diffuse white matter gliosis with increased cellularity, mild astrocyte atypia, and rare mitosis. Other significant features noted include focal dyslamination of the frontal cortex with no hypertrophic neurons or balloon cells, islands of primitive cells in the periventricular frontal white matter, and granule cell dispersion of the hippocampus. These features correlate with the patient's seizures. The examined peripheral nerves revealed no significant pathology and the skeletal muscle histology showed only scattered angulated fibers.

Conclusion: The central nervous system findings including the involvement of the corticospinal tracts supports a neurogenic cause of AMC in WWS, although the pathogenesis of their involvement is unknown.

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Gardner Fibroma and Desmoid-Type Fibromatosis: Lessons from a Pediatric Case with Unique Clinical and Molecular Findings

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Background: Gardner fibroma (GF) is a benign soft-tissue tumor that is associated with a subset of familial adenomatous polyposis (FAP) and can progress to desmoid-type fibromatosis (DF). DF arising from a pre-existing GF (so-called 'GF-DF sequence') is a well-documented phenomenon; however, the pathogenesis of these tumors, particularly the role of *APC* and/or *CTNNB1* mutations in sporadic GF and the GF-DF sequence, remains incompletely understood. Herein, we report a case of DF arising from a longstanding sporadic GF in an 11-year-old boy with unique clinical/radiological, morphological and molecular findings.

Methods: Pathological findings were reviewed and correlated with clinical and imaging findings. Representative discrete tissue areas of GF and DF were identified for molecular genetic testing using the Oncomine Childhood Cancer Research Assay (OCCRA, Thermo Fisher). DNA and RNA were isolated from tissue cores from FFPE blocks as per the manufacturer's protocol.

Results: The patient had a stable, infiltrative fatty lesion of the medial gastrocnemius since late infancy. A muscle biopsy at age 10 showed near-normal muscle fascicles separated by mature adipose tissue with occasional strands of paucicellular dense collagenous fibrosis. After the biopsy, rapid enlargement of the right calf was noted with the development of a well-circumscribed mass. At resection, there was a multilobulated, firm mass (5.5 x 4.5 x 4.5 cm) surrounded by marbled skeletal muscle. Microscopically, the mass consisted of a fibroblastic/myofibroblastic proliferation consistent with DF. Peripheral to the mass and with a well-defined interface, the skeletal muscle showed an infiltrative fibrofatty lesion with areas of plaque-like collagenous fibrosis diagnostic of GF. Although there was no nuclear β-catenin expression in either component, a mutation in CTTNB1 (p.S45F) was identified in both components using the OCCRA. Results were independently confirmed using the Agena MassARRAY sarcoma Panel (V1). After surgery, the patient had a rapid recurrence of the mass. No APC mutation was identified, and there was no family history of FAP/Gardner syndrome.

Conclusion: We describe a unique presentation of GF as an infiltrative deep-seated fatty mass in the distal extremities. This differs from the usual presentation of GF as a plaque-like lesion of the back or paraspinal region and adds GF to the differential diagnosis of an intramuscular fatty lesion. Both the tumor site and the identified *CTNNB1* S45F mutation have been associated with a more aggressive course in sporadic DF. Though to our knowledge, this is the first time a mutation in *CTNNB1* has been identified in GF and GF-associated DF, suggesting that mutational testing should be expanded to include sporadic GF and GF-associated DF.

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Nonspecific Interstitial Pneumonitis: Novel p.E292V / p.K915del Mutation of Adenosine Triphosphate-Binding Cassette Member A3 in a Three-year-old Patient

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Background: Nonspecific interstitial pneumonitis (NSIP) can be related to some common diverse causes, but the adenosine triphosphate-binding cassette member A3 (ABCA3) deficiency with a non infantile presentation is an unusual.

Methods: The patient is a 3-year-old female presenting by low oxygen saturations, respiratory distress, and growth and development failure. She was admitted to the emergency department when she developed a parainfluenza viral infection.
A biopsy of the right apical upper lobe wedge, a chest x-ray, a chest CT, molecular testing, and histological findings were included for diagnosis. Histological findings and a right apical upper lobe wedge resection specimen confirmed the patient has nonspecific interstitial pneumonia. Molecular testing confirmed the p.E292V / p.K915del variant within the ABCA3 gene. The patient was treated and during the follow up period of 10 months, the patient appeared to be doing well.

Results: A biopsy of the right apical upper lobe wedge, a chest x-ray, a chest CT, molecular testing, and histological findings were included for diagnosis. Histological findings and a right apical upper lobe wedge resection specimen confirmed the patient has nonspecific interstitial pneumonia. Molecular testing confirmed the p.E292V / p.K915del variant within the ABCA3 gene. The patient was treated and during the follow up period of 10 months, the patient appeared to be doing well.

Conclusion: We describe a rare case of the ABCA3 gene with an unusual presentation, associated with a novel missense mutation p.E292V / p.K915del condition that creates a deficiency. To the best of our knowledge, ABCA3 deficiency associated with missense mutation p.E292V / p.K915del has not been reported.

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Mandibular High Grade Osteosarcoma Associated with CDK4 and MDM2 Amplification

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Background: Osteosarcoma of the jaw is very uncommon in the pediatric population. While CDK4/MDM2 amplification is typically associated with low grade osteosarcoma of the long bones with or without a dedifferentiated component, their significance is not well documented in osteosarcoma of the jaw.

Methods: Clinical information and radiological data were retrieved from the Electronic Medical Record. Routine and immunohistochemical stains, and Next Generation Sequencing (NGS) were performed.

Results: A 9-year-old male patient presented with a left neck mass. CT and MRI revealed a 5 cm mandibular mass. Pretreatment biopsy showed a hypercellular tumor with sheets of monomorphic polyhedral cells with eosinophilic cytoplasm, ovoid nuclei with fine chromatin and conspicuous nucleoli. There were focal areas with a collagenous and myxoid background but no definite osteoid was appreciated. Mitotic activity was high. Immunohistochemical staining showed that the neoplastic cells were positive for SATB2 (diffuse) and p53 (scattered), and negative for CD99, CK AE1/3, CD34, CD30, synaptophysin, ALK, CD45, S100, SOX10, CD1a, ERG, desmin, Myogenin, MyoD1, SALL4, OCT4, BCOR, Pan-TRK, NUT1 and NKX2.2. NGS panel detected no clinically significant variants but revealed CDK4/MDM2 gene amplification. The overall features were consistent with undifferentiated sarcoma. Following neoadjuvant chemotherapy, a partial resection of the left mandible was performed. The resection specimen showed a tumor composed of pleomorphic malignant cells along with relatively bland appearing sarcomatous cells. Numerous mitoses were present. Malignant osteoid was focally identified. The final diagnosis was high grade osteosarcoma of the jaw.

Conclusion: 1) Jaw osteosarcoma has different characteristics from the conventional osteosarcoma of the long bones, and CDK4/MDM2 amplification may aid in a diagnosis of head and neck osteosarcoma. 2) Histologic and molecular findings (CDK4/MDM2 amplification) in this case suggest that this high grade osteosarcoma may have progressed from a preexisting low-grade osteosarcoma.

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How Many Tests Does It Take to Diagnose a Triple-Hit B-Lymphoblastic Lymphoma? (Hint, It's a Lot)

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Background: *MYC* rearrangements, key features of Burkitt lymphoma, are also seen in several other B-cell non-Hodgkin lymphomas (NHL). In rare instances, they are present in B-cell acute lymphoblastic leukemia/lymphomas (B-ALL/LBL). We present a case of B-LBL with not only an *IGH-MYC* rearrangement but other additional significant genetic alterations.

Methods: A 17-year-old young woman with no notable past medical history presented with bilateral pleural effusions and ascites. Approximately 1 L from each of her effusions was collected and aliquoted for cytology, flow cytometry, cell block, cytogenetics, an RNA fusion panel, chromosomal microarray, and a next-generation DNA sequencing panel. Immunohistochemical studies were performed on the cell block.

Results: Cytology from her bilateral pleural effusions and ascites identified numerous large cells with round to irregular nuclear contours, prominent nucleoli (sometimes multiple), deeply basophilic cytoplasm, and cytoplasmic blebs. Flow cytometric analysis showed an aberrant B lymphoblast population expressing CD19, CD22, cCD79a, normal to mildly decreased CD10, HLA-DR, normal CD45, dim CD71, mildly increased CD38, dim CD58, and TdT, but lacking CD20, surface immunoglobulin, and CD34. Immunohistochemical stains further confirmed lack of CD20 but positivity for BCL-2 and BCL-6. The Ki67 proliferation index was 60-70%. Bone marrow staging showed <1% disease, confirming a diagnosis of B-LBL. She was started on B-LBL therapy. During her induction chemotherapy, ancillary tests were completed. Chromosome analysis showed a complex karyotype including abnormalities notably involving 8q24.2 with a der(14)t(8;14)(q24.2;q32) and an add(18)(q21.?3). Due to these abnormalities, fluorescence in situ hybridization (FISH) was performed, confirming an *IGH-MYC* rearrangement and a *BCL2* rearrangement. Chromosomal microarray corroborated the chromosome imbalances identified in the karyotype including loss of 17pter-p12which includes *TP53*. DNA sequencing additionally showed a *TP53* mutation (NM_000546.5:c.97-1G>A, variant allele fraction 0.93). The RNA fusion panel identified an *IGH-BCL6* fusion.

Conclusion: The combined results are consistent with a B-LBL with *MYC, BCL2,* and *BCL6* rearrangements (triple hit), with a *TP53* mutation that is potentially germline (confirmatory testing pending). With the identification of these alterations, the patient was switched to a mature B-cell NHL chemotherapeutic regimen, as recent studies have shown that *IG-MYC* rearranged B-ALL have an improved response to such therapy. The multimodal diagnostic approach highlights the complexity of this case, with each test uncovering a specific alteration that contributed to the overall diagnosis.

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One Alarming Baby Bump: A Case of Langerhans Cell Sarcoma with OSBPL9-BRAF Fusion Presenting in Infancy

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Background: Langerhans cell sarcoma (LCS) is a rare malignant neoplasm characterized by a neoplastic proliferation of Langerhans cells (LC) with overtly malignant cytology and conspicuous mitotic activity including atypical forms. Most cases of LCS occur in adults, are extranodal and often exhibit multifocal involvement. We present a case of localized LCS in a 6-month-old male with a growing scalp mass, representing to the best of our knowledge, the youngest case with thorough immunophenotypic confirmation and molecular characterization with an *OSBPL9-BRAF* fusion that has not been previously reported in LC tumors

Methods: Hamatoxylin and eosin stained slides were examined. Immunohistochemical staining was performed on formalin-fixed paraffin embedded tissue. Molecular testing was performed by UCSF500 Cancer Gene Test on formalin-fixed paraffin embedded tissue.

Results: A 6-month-old male born at term with no complications and without significant medical history presented with a three-month history of an enlarging left scalp lesion. Ultrasound revealed a heterogenous, hypoechoic scalp lesion measuring 1.3 x 1.3 x 0.5 cm. Clinically, it was thought to be benign and the mass was removed. 2.5 cm skin ellipse with a centrally located 1.3 x 1.0 x 0.6 cm ulcerated nodule and a solid red cut surface was entirely evaluated. Microscopically, sections showed a well-delineated nodular histiocytic neoplasm composed of large mononuclear and multinucleated forms. There was marked nuclear pleomorphism and prominent nucleoli to an extent that is not acceptable for a diagnosis of Langerhans cell histiocytosis (LCH). Conspicuous mitotic activity was noted including few atypical forms. Necrosis was present. By immunohistochemistry the tumor cells were positive for S100, CD1a, langerin, CD68, CD163, and Factor XIIIa (weakly positive). The Ki67 proliferation index was markedly elevated. Immunohistochemistry for BRAF(VE1) was negative. The histomorphology, in conjunction with the immunoprofile of the tumor, confirmed the diagnosis of Langerhans cell sarcoma. An *OSBPL9-BRAF* fusion was identified.

Conclusion: Langerhans cell sarcoma is a rare entity with an incidence of 0.2 per 10,000,000 and less than 100 cases reported in the literature with few cases reported in children. Recurrent activating mutations involving MAPK and PI3K-AKT signaling pathways have been recently discovered in histiocytic neoplasms with BRAF V600E mutations in up to 57% of LCH cases. OSBPL9-BRAF fusion has only previously been identified in papillary thyroid carcinoma and is a novel finding in LC tumors. The differential of LCS includes other malignant histiocytoses such as histolytic sarcoma as well as anaplastic large cell lymphoma, atypical epithelioid histiocytoma and juvenile xanthogranuloma.

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Rosai-Dorfman Disease with Features of IgG4-Related Disease in the Breast: A Case Report and Literature Review

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Background: Rosai-Dorfman disease (RDD) typically occurs in lymph nodes where it is characterized by a histiocytic sinusoidal expansion. These histiocytes display prominent nucleoli and abundant cytoplasm with engulfed lymphocytes and plasma cells, and stain with S-100 and histiocytic markers, but are negative for CD1a. When RDD involves extranodal sites the typical locations include the skin, soft tissue, orbit, bone, and upper respiratory tract. RDD of the breast without nodal involvement is extremely uncommon, with less than 50 reported cases, and has mainly been seen in adults. Mammary RDD manifests as mass lesions and may involve axillary lymph nodes. In the breast RDD may have histopathological overlap with IgG4 related disease (IgG4-RD). IgG4-RD is characterized by lymphoplasmacytic infiltrates, IgG4/IgG cell ratio greater than 40%, obliterative phlebitis and storiform fibrosis. A serum IgG4 level above 135 mg/ml is supportive of the diagnosis. IgG4-RD in the breast is reported as IgG4 related sclerosing mastitis. Only 3 cases of mammary RDD with features of IgG4-RD have been reported in adults.

Methods: The electronic medical record and pathology records were reviewed. Routine and immunohistochemical stains were performed on the excision specimen. The authors reviewed the literature on RDD and IgG4 plasma cell abnormalities in the breast.

Results: A 20 year old female with a history of juvenile granulosa cell tumor 4 years prior presented with a 9 cm breast mass. Histologic examination demonstrated breast parenchyma involved by a dense chronic inflammatory infiltrate composed of histiocytes, plasma cells and lymphocytes. The histiocytes were large and polygonal with abundant eosinophilic cytoplasm and large vesicular nuclei. Numerous histiocytes contained engulfed lymphocytes and plasma cells. Focal fibrosis was present. However, obliterative phlebitis was not identified. The histiocytes were positive for CD68 and CD163. Many of the larger cells were S100 positive which highlighted the emperipolesis. They were negative for Langerin. There was a large plasma cell population. IgG4 stained approximately 45% of the IgG+ plasma cells. A diagnosis of Rosai-Dorfman disease of the breast with features of IgG4 related disease was made.

Conclusion: RDD with associated IgG4 related disease of the breast is rare and only reported in adults. This is the youngest case of this entity in the English literature. It is important to be able to recognize and differentiate it from other histiocytic processes that can occur in the breast.

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Non-Bacterial Thrombotic Endocarditis in a 7-year-old Boy With Osteosarcoma

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Background: Non-bacterial thrombotic endocarditis (NBTE), first described in 1888 by Zeigler is a rare condition characterized by sterile friable cardiac valve vegetations seen in association with autoimmune diseases and malignancy. Incidence increases with age and those seen in neonates are right-sided valve lesions in association with intracardiac catheters, persistent fetal circulation and disseminated intravascular coagulation. Older children often have vegetations on the aortic and mitral valves (MV) in association with malignancy, hypercoagulable states or septicemia. Although rare, NBTE is a serious and potentially underdiagnosed manifestation that can cause substantial morbidity due to systemic emboli, seen in about 40% patients, most notably multiple ischemic cerebrovascular strokes. Diagnosis often requires high degree of clinical suspicion.

Methods: 7-year-old boy with history of infantile hemangioma, HSV positive facial lesion, 6 weeks of right leg pain with limping, acute onset nausea, vomiting, headache and fatigue since 3 days presents at an outside hospital in altered mental status. X-ray knee & pelvis a month ago at an outside hospital were normal. Lab tests revealed elevated ALT, AST and AKP. CT Head without contrast showed cerebral edema in the posterior left frontoparietal and occipital lobes. Upon transfer of care to our hospital, X-ray right femur showed aggressive periosteal reaction in mid/distal diaphysis, concerning for osteosarcoma/ osteomyelitis, confirmed as high-grade osteosarcoma on biopsy. CT & MRI Head showed multifocal ischemic infarcts in the temporoparietal and occipital lobes, concerning for an embolic phenomenon. Echocardiogram revealed a 5 mm pedunculated mass on the posterior leaflet of MV. Despite maximum conservative measures, general condition worsened with additional intracranial infarcts with cerebellar tonsillar and uncal herniation and he eventually succumbed to the disease.

Results: Postmortem examination confirmed the clinical impression: i) 7 cm, firm, tan brown tumor in mid to distal femur with 20-30% necrosis, ii) Fibrin thrombus on the posterior leaflets of MV measuring 1.0 cm with associated left ventricular hypertrophy and mild fibrotic changes in the MV and triscuspid valves, iii) Ischemic infarcts in bilateral kidneys, iv) ischemic infarct in spleen

Conclusion: This is a case report of high-grade osteosarcoma of the right femur in a 7 year old boy (younger than typical age:10 -25 yrs) complicated by NBTE and presenting with multiple ischemic infarcts in the brain, bilateral kidneys and spleen. Acute onset neurologic symptoms in a child with no significant past medical history should alert the clinicians to perform detailed work-up for a cardiac source in the clinical setting of infective endocarditis, primary cardiac tumors or NBTE.

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Umbilical Cord Length in the Pathogenesis of Maternal Vascular Underperfusion and Stillbirths in Singleton Gestations

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Background: Per U.S 2016 National Vital Statistics Report, complications of placenta, umbilical cord (UC) and fetal membranes is the leading cause of death (COD) between 29-40 weeks of gestation. In the obstetric literature, minimum 32 cm of UC length is required for normal fetal descent. Fetal movements increase during the course of pregnancy and it decreases and increases with shorter and longer UCs, respectively. However, we hypothesized that increased fetal movements in a singleton gestation with short UC would predispose to uteroplacental hypoxia or maternal vascular underperfusion (MVU) due to abruptio placentae or villous infarcts, complicating pregnancy outcomes including stillbirths.

Methods: In this retrospective study, 82 cases of stillbirths from singleton gestations between 29-40 weeks were retrieved from the pathology database of a tertiary care center. The COD, maternal, fetal risk factors, gross and microscopic findings in placenta, UC and fetal membranes were tabulated. Of note, length of UC attached to the fetus was also included. A pathologist blinded to COD, maternal, fetal risk factors and UC length marked the placentas with pathologic evidence of MVU (PMVU) based on weight of placenta (small/ appropriate/ large) and pertinent gross and microscopic findings. Data was analyzed to obtain the mean length of UC and its statistical significance in PMVU and stillbirths.

Results: PMVU was identified in 37/82 stillbirths (45%) with a mean UC length of 35.1 cm, out of which 15 (40.5%) were associated with maternal history of hypertension. Mean UC length in 30 stillbirths with COD attributed to clinical history or PMVU (36.5%) is 35.0 cm. UC length of less than (<) or equal to (=) 35 cm is found to have statistical significance in stillbirths with PMVU (p = 0.0017) and COD attributed to clinical history or PMVU (p=0.0243). UC length < or = 35 also increase the risk of COD due to MVU in hypertensive singleton gestations (p=0.0463).

UC length (cm)	Number of still births with PMVU	Hypertension & PMVU	COD attributed to clinical history or PMVU
50- 60	4	1	2
40- 50	11	5	9
30- 40	9	4	11
20- 30	10	2	5
10- 20	2	2	2
< 10	1	1	1
Total number of cases	37	15	30
Mean UC length (cm)	35.1	33.2	35.0

Conclusion: This study indicates that UC length of < or = 35 cm is an independent and contributory risk factor to hypertension in the pathogenesis of MVU. We recommend documentation

of UC length and close surveillance of singleton gestations with UC length < or = 35 cm and associated maternal risk factors of MVU, to prevent adverse pregnancy outcomes including stillbirths.

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Villitis of Unknown Etiology: Exploring Recurrence Rates and Co-morbid Placental Lesions in a Setting of Preeclampsia and Intrauterine Growth Restriction in Eastern Ontario

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Background: Villitis of unknown etiology (VUE) is a common inflammatory lesion of the placenta, affecting approximately 7% – 33% of pregnancies. VUE has been observed extensively in pregnancies affected by preeclampsia (PE) and intrauterine growth restriction (IUGR), with varying co-morbid placental lesions observed in these cases. VUE demonstrates a significant recurrence risk in subsequent pregnancies (10%-38%).
In our Eastern Ontario cohort, we seek to comprehensively: (1) describe the recurrence rate of VUE in subsequent pregnancies; (2) identify changes in distribution, location or severity; and (3) explain co-morbid placental lesions that coincide with a diagnosis of VUE, and any differences between our PE/IUGR subset and our reference group.

Methods: Each placenta with PE and IUGR was identified via EPIC-Hyperspace from 2013-2019 and VUE cases were subsequently identified. Approximately double the number of cases were included as references. The reference group consisted of placentas with confirmed villitis pathology, but without clinical diagnosis of PE or IUGR. One pathologist examined each case to diagnose VUE according to our synoptic placental pathology form and the Amsterdam Working Group criteria. Details of location, severity and coverage were noted, along with an assessment of additional placental lesions. All study data was securely stored in our REDCap database. Recurrence rates of VUE in our Eastern Ontario cohort were evaluated via EPIC-Hyperspace.

Results: In our cohort, 2825 placentas were identified with PE and IUGR and 242 with VUE. There were 45 PE/IUGR cases and 83 reference cases outside the setting of PE and IUGR, which resulted in a total of 128 examined cases. There were 12 recurrent cases of placental pathology, and of these, 3 were diagnosed with VUE. Our PE/IUGR group had increased prevalence of high-grade, multifocal, non-basal villitis. The PE/IUGR group also had increased prevalence of various inflammatory, MVM and FVM lesions, including PVD, avascular villi and obliterative endovasculitis when compared to the reference group. The recurrence rate of placentas sent to pathology was 9%, and of these, 25% had recurrent VUE. There were no notable differences in villitis pathology among the recurrent cases.

Conclusion: A clinical diagnosis of PE and IUGR could indicate VUE severity, distribution, location, and frequency of various associated lesions, although further investigation is needed. Results of this study may aid pathologists and obstetricians to individualize management strategies for treating VUE.

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Placental Mesenchymal Dysplasia in Twins (With a Fetus and a Complete Mole) Contrasted with Placental Mesenchymal Dysplasia Detected Early in Pregnancy without a Fetus

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Background: Placental mesenchymal dysplasia (PMD) almost exclusively presents with a fetus. Contemporary literature highlights the mosaic nature of these placentas by demonstrating loss of p57 nuclear staining in villous stromal cells but not villous cytotrophoblasts. While the findings in an early complete mole are recognized, the findings to identify an early PMD are limited.

Methods: Gross specimens and glass slides from two cases with PMD were reviewed. **Case 1** was a twin comprised of a fetus with associated PMD and an adjacent discrete mass, a complete hydatidiform mole (CHM). **Case 2** was products of conception – an original D & C and retained products expanded 10 weeks later. Both cases were studied with STR and p57 IHC. Case 2 was additionally stained with p63, beta-catenin, e-cadherin, human placental lactogen, beta-HCG, inhibin, and SALL-4.

Results: **Case 1:** The histologic appearance of the PMD and CHM were classic and stained appropriately with p57. STR data was generated from maternal and paternal blood, umbilical cord, placenta, and mole. The mole was diandric diploid, and the PMD showed a maternal haploid component over the same diandric pattern as the mole with proportions consistent with PMD.

Case 2: The primary D&C was composed mostly of large mesenchymal villi with thin layers of cytotrophoblasts and syncytiotrophoblasts, with occasional central cisterns, and without trophoblastic hyperplasia. P57 was lost in stromal nuclei and retained in villous cytotrophoblasts.

A smaller population of villi had features consistent with a complete mole - stromal cell apoptosis and appropriate loss of p57. Oddly, these villi were characterized exclusively by cytologically atypical cytotrophoblasts (p16 positive) that were also SALL-4 positive, and trophoblastic hyperplasia was not seen. This is a pattern seen focally in a classic CHM where marked trophoblastic hyperplasia predominates.

The retained products were entirely PMD, and this was reflected in the STR that showed a greater paternal contribution in the primary specimen vs the retained material. Occasional villi from the retained material showed a striking subtrophoblastic branching vascular plexus.

Conclusion: 1. That a POC without fetal tissue harbors PMD may not be obvious, and liberal use of p57 may be required to identify these cases.

2. Central cisterns and subtrophoblastic vascular proliferation may be a flags for early PMD without a fetus.

3. It is unclear in Case 2 if the findings represent twins or generation of a mole within a mosaic conception. The 2 cases presented may be at 2 ends of a spectrum.

4. This report should raise awareness to the possibility of early PMD and the possibility of a coexisting molar phenotype that may be highlighted more by frank cytologic atypia than by trophoblastic hyperplasia.

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Fetal Maternal Hemorrhage Mapped in a Placenta from a Case of Fatal Fetal Maternal Hemorrhage

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Background: Fetal maternal hemorrhage is a recognized cause of fetal demise and classically presents with a fetus that appears pale and exsanguinated and a mother with an abnormal level of circulating fetal erythrocytes. Not much is known about the dynamics of FMH, and mapping of a placenta in a case of fatal FMH was done to determine if such mapping could detect FMH, quantify it, and possibly explain the etiology.

Methods: Autopsy results as well as the mother's Kleihauer-Betke (KB) result were reviewed to confirm the cause of death. The placenta was mapped by taking 33 sections at regularly spaced intervals for morphologic evaluation and then studying a subset of 4 sections with an immunostain for hemoglobin F – FITC conjugate (HbF). A dual band pass filter was used, and the maternal erythrocytes (RBCs) exhibited red autofluorescense. The fetal RBCs exhibited bright green fluorescence. Fields were evaluated for the percent of fetal RBC present.

Results: A total of 2322 fields were evaluated, and 246 images were captured. Most fields showed no fetal RBCs in the intervillous space (in contrast to those in the fetal circulation, an internal control). Large numbers of fetal RBCs (5 percent or more) were seen only in clusters or clots, primarily in the subchorionic or juxtabasal zones. The 33 map sections plus 5 additional sections did not show pathology to explain the bleed. The KB was 9%.

Conclusion: 1. Blood flow in the intervillous space did not reflect an even dilution of fetal RBCs reflective of the KB possibly due to artifactual elution of the intervillous space.
2. The sequestration of fetal RBCs in aggregates may be predictive of the KB, but a study of multiple cases and controls would be required to test that hypothesis.
3. IHC using an alkaline phosphatase reporter would be a more appropriate method for a larger series.

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Prevotella Melaninogenia as an Unusual Cause of Congenital Pneumonia in a Twin Pregnancy Complicated by Vaginal Bleeding

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Background: Congenital pneumonia (CP) occurs in 10% of preterm infants and contributes to 5-10% of neonatal deaths. Most infections are acquired via intrauterine aspiration of infected amnionic fluid, and organisms such as *E. coli* and GBS predominate. Here we present the autopsy findings of an 8-hour old male neonate who died of pneumonia. He was Twin A of a diamnionic dichorionic (di-di) twin pregnancy delivered at 24 weeks 4 days gestation via Cesarean section to a 35-year old G6P1143 female. The pregnancy had been complicated by placenta previa, vaginal bleeding, and cerclage placement. After an episode of PPROM and increased vaginal bleeding, decision was made to proceed with delivery.

Methods: Autopsy and placental examination were performed. Hematoxylin and eosin (H&E) as well as Brown and Hopps (B&H) stains were performed. Lung tissue was submitted for bacterial culture.

Results: Autopsy revealed a male neonate with growth and maturation appropriate for 24 weeks gestation. No major congenital anomalies were identified. Grossly, acute bilateral pulmonary hemorrhage was present. Patchy bilateral acute CP was seen on H&E, and B&H stain showed Gram-negative rods in airspaces. Bacterial cultures from lung tissue grew *Prevotella melaninogenica*. Additionally, acute inflammatory cells were seen within stomach contents with B&H showing Gram-negative rods. The placenta showed a fused di-di twin placenta with weight appropriate for gestational age. Mild patchy acute subchorionitis without a fetal acute inflammatory response was identified in the placenta of Twin A. However, a 2.6 cm acute to remote marginal hemorrhage was identified, and large clusters of Gram-negative rods and Gram-positive cocci were seen within the hemorrhage on B&H stain.

Conclusion: The autopsy findings are consistent with congenital pneumonia acquired via an ascending infection from the vagina. The presence of *Prevotella melaninogenica* is unusual, as this anaerobic organism is a known vaginal commensal, but to the best our knowledge, it has never been reported in association with congenital pneumonia. *Prevotella spp.* require hemin as the source of iron for growth and bind lactoferrin that is released with the contents of neutrophils during inflammation and bleeding. In this case, antepartum episodes of vaginal bleeding and/or cerclage placement may have contributed to vaginal dysbiosis with overgrowth of *Prevotella spp*. It is likely that the bacteria seeded the marginal placental blood clot and then ascended into the amnionic fluid. Selective infection of amnionic fluid surrounding twin A, while sparing twin B, highlights the unique vulnerability that close proximity to birth canal imposes on twin A in ascending infection.

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Placental Metastasis of Breast Carcinoma with Abnormal Non-invasive Prenatal Screening: A Case Report

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Background: Placental metastases from maternal malignancies are exceedingly rare. The most common malignancy to metastasize to the placenta is malignant melanoma. There are also reports of metastases from hematologic malignancies, pancreatic, breast and lung cancers. Metastasis to the placenta typically portends a poor prognosis for the mother.

Methods: Our patient is a 36-year-old G2P1001 female with a history of right sided breast cancer who presented with shortness of breath and tachycardia and underwent an emergent caesarean section at 33.5 weeks gestation. Her initial diagnosis was 4.5 years prior, detected by the patient while nursing after her first pregnancy. Her pathology was invasive ductal carcinoma, grade 3, ER/PR negative and HER2 3+. There was extensive lymphovascular invasion and axillary lymph node metastases. She was treated with neoadjuvant chemotherapy followed by a right mastectomy, radiation and trastuzumab, completed 3.5 years prior to the current pregnancy. Non-invasive prenatal screening (NIPS) performed at 11 weeks gestation revealed multiple genome wide chromosomal aberrations, suggestive of maternal malignancy, however imaging performed at that time was negative. Following delivery, she was found to have pleural, pericardial, brain and bone metastases.

Results: Upon gross examination, the placenta weighed 357 grams and had a peripherally inserted umbilical cord. Histologic examination demonstrated multiple foci of clusters of atypical cells with large nuclei, irregular nuclear membranes and prominent nucleoli. The clusters were present in the intervillous space, without involvement of the villous stroma. The cells showed positivity for mammaglobin and HER2 (3+), consistent with metastatic invasive ductal carcinoma. Evidence of fetal vascular malperfusion (mural fibrin deposition and small foci of avascular villi) were also present.

Conclusion: Metastatic disease to the placenta is rare, but can be seen. Our case is of particular interest due to the detection of recurrence by NIPS prior to radiologic recurrence, and the massive spread of disease during pregnancy, especially considering the tumor's ER/PR negative status. In women with a history of malignancy, thorough examination of the placenta for metastatic disease should be performed. Identification of metastatic disease will raise the mother's stage to IV and has been associated with a high mortality rate.

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Fetal Hydrops with Anhydramnios Secondary to Abdominopelvic Sacrococcygeal Teratoma

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Background: We present the case of a fetus delivered at 29 weeks gestational age following termination of pregnancy (TOP). During the course of routine prenatal examinations, ultrasound imaging revealed a female fetus with markedly abnormal intra-abdominal anatomy and a heterogeneous abdominopelvic mass in the setting of anhydramnios. The parents were counselled regarding poor prognosis secondary to lung hypoplasia and opted for TOP.

Methods: A standard autopsy (excluding brain examination) was conducted.

Results: At autopsy, fetal weight was 2048 g (expected for gestational age, 1230+/-225g). The abdomen was tensely distended. The periorbital, perineal, and perianal areas were all edematous. There was placentomegaly (482g, 90-95th percentile for gestational age). Internal examination showed a 268 g mass entirely occupying the pelvis and lower abdomen. The descending and sigmoid colon were significantly dilated and appeared to merge with the tumor, terminating in a blind end. The bladder outlet also tapered into a blind end. Elsewhere, thoracic findings included cardiomegaly (heart weight 11.6 g, expected for gestational age, 3.6+/-1.3g) and pulmonary hypoplasia (combined lung weight, 11.6 g, expected, 30.2+/-9.5g). There were small serous pleural and pericardial effusions.

The tumor contained derivatives of all three germ layers. There was abundant primitive neuroectoderm without evidence of malignant germ cell component on H&E or immunostains. There was persistent/exaggerated extramedullary hematopoiesis, including in the liver, spleen, and heart. Lung maturation was delayed, reaching only the late canalicular stage of development.

There was normal ploidy of chromosomes 13, 18, 21, and X (rapid aneuploidy detection) and no relevant genomic deletions or duplications (microarray). Specific MNX1 testing is pending referral to medical genetics for appropriate counselling.

Conclusion: This case of Altman type IV SCT (predominantly intrapelvic tumor without external component) provides an excellent example of clinical-radiological-pathological correlation. Although we could not confirm a familial/genetic link in this case, the diagnosis of presacral SCT should prompt consideration of molecular testing to elucidate a potential underlying genetic etiology and consequent risk of recurrence.

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Florid *Bacillus Cereus* Infection of the Placenta Associated with Intrauterine Fetal Demise

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Background: *Bacillus cereus* is a gram-positive, rod-shaped bacterium that is commonly implicated in foodborne illness but has also become increasingly recognized as a source of serious non-gastrointestinal infections, including sepsis, meningitis, and pneumonia. These infections have been described in the pediatric population, and especially the neonatal population; however, there are no previously described cases of fetal demise associated with *Bacillus cereus* infection of the placenta.

Methods: We present a case of acute chorioamnionitis-related intrauterine fetal demise of twin A at 17 weeks gestation, noted two days after selective termination of twin B.

Results: Histological examination revealed numerous gram-positive bacilli in the setting of severe acute necrotizing chorioamnionitis and subchorionitis, intervillous abscesses, acute villitis, and peripheral acute funisitis. Microbiology testing of maternal blood and placental swab specimens were both positive for *Bacillus cereus*.

Conclusion: This case underscores the importance of recognizing *Bacillus cereus* as a human pathogen, and specifically demonstrates its potential as an agent of severe intraamniotic and placental infection with poor outcomes for the fetus.

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Congenital Pulmonary Lymphangiectasia - A Rare Cause of Fetal Hydrops

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Background: The major diagnostic challenge in cases of hydrops fetalis is to establish the underlying aetiology amongst the wide range of conditions which can potentially result in accumulation of extra-fluid.

Methods: Here we present a case of foetal death in-utero at 23 weeks gestation with ultrasound detected foetal hydrops which was first diagnosed in the initial scan at 13 weeks. The morphology scan also raised the possibility of cardiac abnormalities.

Results: Macroscopic post-mortem examination of the foetus only confirmed hydrops, but no other recognisable structural abnormality was detected. Marked autolysis made detailed examination of heart difficult. Histological examination of lungs showed diffuse changes indicative of congenital pulmonary lymphangiectasia (CPL). There was no evidence of infectious process. Molecular karyotyping revealed no clinically significant copy number changes with long continuous stretches of homozygosity.

Conclusion: CPL is a rare developmental disorder which presents in-utero or early childhood and is associated with non-immune hydrops. The importance of histology in the fetal postmortem examination is often overshadowed by internal dissection and placental studies, especially in cases where the organs are severely autolyzed due to delays in examination or prolonged fetal death in-utero. This case report highlights the importance of microscopy in the complete foetal post-mortem examination.

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Renal Tubular Dysgenesis (RTD) Associated with Severe Placental Maternal Vascular Malperfusion

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Background: Renal tubular dysgenesis (RTD) is a fatal rare disorder characterized by diminished to absent differentiation of proximal convoluted tubules and anuria leading to oligohydramnios. RTD has both genetic and secondary causes. Primary causes are heterogeneous mutations of genes acting in the renin-angiotensin system (RAS). Secondary RTD can be caused by decreased renal perfusion in utero. We present a 2-day old female infant born to an 18-year old G1P0 mother by emergency cesarean section at 26 weeks gestation because of preeclampsia, oligohydramnios, intrauterine growth restriction and decreased fetal heart rate variability. The infant developed severe metabolic acidosis and hypotension, which was refractory to medical treatment, and eventually expired.

Methods: Autopsy and placental examination were performed. H&E and CD10 immunohistochemical stains were performed.

Results: Autopsy revealed a small for gestational age infant with no major gross congenital anomalies or evidence of infection. The kidneys appeared grossly unremarkable; however, microscopic examination of the kidneys revealed crowding of glomeruli in the cortex, and paucity of proximal convoluted tubules. This was confirmed by a significantly reduced number of CD10-immunoreactive tubules compared to an age matched control. Other autopsy findings included hyaline membrane disease, germinal matrix hemorrhage, patchy atrophy of the skin, petechial and visceral acute hemorrhages, and stress involution of the thymus and adrenal glands. The placental examination showed a small placenta for 26 weeks gestational age and severe maternal vascular malperfusion (MVM) including villous infarcts and acute atherosis/fibrinoid necrosis in parietal arterioles.

Conclusion: This premature, growth restricted infant had multiple significant complications related to premature birth, and the autopsy uncovered an unexpected finding: renal tubular dysgenesis. The underlying etiology of RTD in this case is not certain, but the evidence of growth restriction and fetal stress at autopsy supports the hypothesis that placental insufficiency secondary to MVM initiated the pathology, leading to fetal hypoxia, hypoperfusion of the fetal kidneys and ultimately development of RTD. The normal function of RAS to maintain arterial blood pressure and vascular homeostasis may explain why hypotension was intractable in this patient. Our case demonstrates how placental pathology can contribute to the pathogenesis of RTD and the importance of placental perfusion for the health of the fetus.

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Localized Exuberant Osteoblastic Proliferation of Newborn: a Potentially Newly Described Bone Lesion

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Background: Osteogenesis is a complex system, especially active in the neonatal period. Both malignant and benign bone-forming tumours of childhood are rare, with peak incidence in adolescence, and flat bone tumours being especially uncommon.

Methods: Pathology samples were sent for evaluation by expert bone pathologists at our institution, Boston Children's, and John Hopkins medical institutes. We summarize the clinicopathologic implications.

Results: A baby boy born at 33 weeks and 6 days gestation following an uncomplicated pregnancy was found to have a left pre-auricular lesion at day of life 14. Lesion was hard, nonmobile, and nontender, with ill-defined margins, and no overlying skin changes. Rapid extension nasally was concerning for malignancy. Imaging revealed a sclerotic bony mass with heterogeneous enhancement and spiculated borders overlying the squamous portion of the temporal bone, with no intracranial extension. Bone scan was normal. Differential diagnosis was broad, including osteoblastoma and chondroblastoma. Pathology revealed plump uniform osteoblasts with round eccentric nuclei and abundant eosinophilic cytoplasm in a mineralized matrix, with no cytologic atypia. Cells had diffuse positivity for CD99, SMA, and vimentin, and focal positivity for CD56, with retained INI1 expression. Cells had a high proliferation index. Cells were negative for AE1/AE3, CK903, CK818, CD68, CD1A myogenin, MYOD1, myoglobin desmin, S100, HMB-45, MEL-A, CD45, CD3, CD20, MUM1, myeloperoxidase, and ALK protein expression. FISH for EWSR1 was also negative.

It was concluded that stable radiographic and clinical appearance, and difficulty of achieving negative surgical margins, allowed for conservative management with close follow up. Repeated CT at 15 months of age showed involution of bone spiculations and further formation of normal medullary bone. The lesion clinically involuted over 21 months. Aside from mild language delay, his development is normal.

Given spontaneous involution and pathologic features, diagnostic considerations include osteoblastoma and chondroblastoma (with pathology reports split between these two diagnoses), and well differentiated low grade osteosarcoma. However, none of these entities are known to involute – single system LCH has been reported to involute, although the clinical picture is not in keeping with this diagnosis. Thus this is a highly unusual primary bone lesion best described as a lesion of exaggerated osteogenesis, with no clear trigger for aberrant growth.

Conclusion: To the best of our knowledge, we describe a heretofore unreported lesion of localized exuberant osteoblastic proliferation with spontaneous involution. Its description could have management implication of similar lesions, to prevent an unnecessary major and potentially mutilating resection.

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Umbilical Cord Nevi - A Rare Finding with Implications for Prenatal Nevogenesis and Cord Lengthening

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Background: Congenital melanocytic nevi (CMN) occur in 1% of newborns; 3% have multiple foci. We present a rare case of noncontiguous nevi of the umbilical cord (UC). The newborn had a large left chest and arm nevus. A single previously reported case of UC nevus involved direct extension of a giant periumbilical nevus. Other reports of fetal nevomelanocytic placental involvement showed microscopic foci restricted to villous stroma and vessels. We submit our case supports both prenatal origin of CMN and the manner by which UC lengthening appears to occur.

Methods: Standard placental examination, histology, and immunostaining were performed. The term placenta was 457g (426–611g expected) with a trivascular, eccentric,16 cm long, 1.4 cm diameter UC (2 coils/10cm) and a separate 15.5 cm UC segment. Fetal ends of the segments showed noncontiguous brown maculae with speckling, grayish maculae, and pigmented linear foci; lesion contours followed cord spirals. The membranes, chorionic plate, and parenchyma showed no pigmented foci.

Results: Microscopically, UC lesions showed nevoid melanocytes, intra-amniotic melanocytes and amniocyte cytoplasmic melanin granules. Amnion and Wharton's jelly had small nevomelanocyte nests and single cells; there was no cytologic atypia. The UC insertional end, chorionic plate and villous tree showed no nevomelanocytes or melanin pigment. Melan-A (MART-1) immunostain (red chromogen) showed cytoplasmic expression in amniocytes and stromal melanocytes.

Conclusion: Epidermal melanocytes arise from stem cells of neural crest (NC) origin. Deep NC-derived nerve sheath cells present at 6 weeks of developmental age (wk) give rise to nevus stem cells through 12 wk. Stem cells migrate along deep nerve axons and branch axons to the superficial dermis. They proliferate and differentiate into nevomelanocytes and ascend to the epidermal junction. Nevogenesis of CMN likely represents aberrant nevus stem cell differentiation and proliferation during early embryogenesis, cluster migrations along deep nerves, and irregular widespread distribution of occult clusters in embryonic skin and soft tissue.[Cramer S. Am J Dermatopathol 2012;34:60] Our case supports this model. The UC forms by 5 wk, spans the amnioectodermal junction of the embryo to the placenta, is "cloaked" in amnion by 12 wk and not innervated. Thus, we propose occult nevus cell nests were likely present in periumbilical stroma that is continuous with what becomes Wharton's jelly, and that melanocytes later ascended to the amnion. We also propose the spiraled noncontiguous distribution of the nevi supports the concept that UC lengthening occurs along the pitch of cord coils.

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Triplets Comprised of a Normal Fetus, Abnormal Fetus with a Partial Mole and a Complete Mole. STR Analysis and Proposal of Complex Mitotic Spindles

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Background: Twins that include a complete and/or partial mole are rare but well represented in the literature. Study of these cases provides data that adds to our knowledge of pronuclear fusion anomalies that produce these interesting conceptions. In the case presented, we report a triplet comprised of a karyotypically normal fetus (NF), a stillborn abnormal fetus with a partial mole (PM), and a complete mole (CM). Conception was assisted by follicle stimulation and intrauterine injection. A prior pregnancy produced a normal infant. This is the first reported case of triplets containing 2 moles.

Methods: This case was analyzed by reviewing medical records, the gross specimen, light microscopy, and STR data that used 15 autosomal markers. Blocks used for STR were dissected for enrichment. Samples studied included: 1 NF kidney, 1 NF placenta, 2 PM and 3 CM.

Results: Ultrasound showed 3 gestations with 2 fetuses and a CM. Chorionic villous samples from the placentas with fetuses showed 46XY (normal male) and 70XXXY (triploid with extra X), respectively. No karyotype was obtained for the CM. Products of conception were delivered by dilatation and extraction. Gestational ages, by foot length, were 17 weeks (46XY) and 12.4 weeks (70XXXY). PM triploidy was confirmed by FISH, and the CM was confirmed with p57 IHC. STR analysis indicated that the triplets were the products of two maternal pronuclei (m1, m2) and two paternal pronuclei (p1, p2). When a parent is homozygous for an allele, it is described as m or p. Seven markers were partially uninformative (m1pp x 2, m2pp x 2, mp1p1, and mp1p2 x 2). The presence m1 and m2 in the partial mole was determined by comparing the 46XY gestation to the partial mole. Partial mole STR showed m1p1p1, m1p1p2, m1p2p2, m2p1p2, and m2p2p2. The complete mole showed the presence of p1 and p2, although heterozygosity (p1p2) could not be distinguished from a mixture of homozygous contributions (p1p1 and p2p2).

Conclusion: 1. STR analysis indicates that 2 maternal and 2 paternal pronuclei formed the partial mole.

2. This pregnancy could have been the product of 1, 2, or 3 eggs with requisite number of pronuclear duplications required to populate the below described mitotic spindles.

3. 1 egg would require a separation of the NF followed by octopolar mitoses after segregation of M1 and M2.

4. 2 eggs might be either:

(a) a biparental diploid egg and an egg with octopolar mitoses (as in “3”), or

(b) a partial mole with 2 tetrapolar mitoses and twin (NF/CM) from a pentapolar mitosis.

5. 3 eggs would be diploid biparental, partial mole (2 tetraploid mitoses) and complete mole (1 tetraploid mitosis).

6. The 3 egg theory appears most likely due to highly speculative nature of the octopolar spindle.