

Platforms - Session 1

Abstract 1-

Ljungan Virus Antigen Detected in Brain and Spinal Cord from Cases of Stillbirth

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Background: Current estimates of the incidence of stillbirth in the United States are of about 27,000 cases per year, making stillbirth accountable for approximately half of all perinatal deaths.

An association of cyclic wild rodent abundance with incidence of intrauterine fetal death (IUFD) in humans has been reported in Sweden, which supports the hypothesis of a zoonotic disease as causative agent of stillbirth. Ljungan virus (LjV) was detected by immunohistochemistry (IHC) in placenta and brain of approximately half of the Swedish IUFD cases investigated. Ljungan virus, a parechovirus in the Picornaviridae family, has been isolated from wild rodents and is present not only in Sweden but also in many other countries including the U.S.

This study reports a preliminary investigation of LjV in a stillbirth case series from the Texas Gulf Coast region.

Design: Seventeen cases of stillbirth and 14 controls (therapeutic abortions or accidental deaths) were selected from an autopsy case series and examined by IHC. Unstained sections were prepared from paraffin blocks of brain and spinal cord collected at the time of post-mortem examination. Immunostaining was performed as previously described. Presence of LjV specific antigen was detected with two different mouse monoclonal antibodies, using normal mouse serum as a control. Tissues from LjV infected and non-infected animals were also included as antigen staining controls. Two-tailed Fisher's exact test was used to determine statistically significant differences between cases and controls.

Results: Immunostaining performed on the brain sections detected LjV antigen in 8 out of 17 cases of IUFD, as opposed to none of the controls (p-value 0.003). When sections of spinal cord were also included, 11 of 17 IUFD cases tested positive, compared to 3 of 14 controls (p-value 0.029). Intense staining was mostly localized in nerve processes, and occasional staining was observed in neuronal cell bodies in the medulla.

Conclusions: As previously described in a Swedish case series, Ljungan virus appears to be more prevalent among cases of stillbirth, compared to cases of terminations/accidental deaths. However, it is unclear exactly which strain of LjV was detected – whether the original strain isolated in Sweden or a 'Ljungan-like' virus like those previously isolated in wild rodent populations in the U.S. Future investigations will include virus isolation and sequencing to determine the exact strain of LjV circulating in the area.

Abstract 2-

Immunohistochemical Expression of SALL4 in Wilms Tumors, Nephrogenic Rests, and Fetal and Postnatal Renal Cortices

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Background: SALL4 is a novel transcription factor that plays a role in the maintenance of stem cell pluripotency. SALL4 has been suggested to be a sensitive and relatively specific marker of malignant germ cell tumors, but may also be expressed by non-germ cell tumors such as carcinomas, sarcomas, primitive neuroectodermal tumors, and ovarian clear cell carcinomas. SALL4 is important in renal development and its mutations give rise to renal malformations as part of multiple congenital anomaly syndromes such as Duane-radial ray syndrome and the IVIC syndrome. Because Wilms tumor recapitulates developing kidney, we hypothesized that Wilms tumor cells may express SALL4.

Design: Immunohistochemistry for SALL4 was performed on tissue microarray sections of 52 Wilms tumors, 6 nephrogenic rests, and 13 fetal renal cortices spanning 15 to 39 weeks' gestation. All TMA sections contained cores of non-neoplastic postnatal kidneys as controls. Appropriate positive and negative controls were performed with each run of immunostains.

Results: 26 of 52 (50%) Wilms tumors showed SALL4 immunoreactivity, ranging from strong and diffuse to focal and weak. Blastemal, epithelial, and combined blastemal and epithelial patterns of immunoreactivity were identified. No cases showed stromal reactivity. In the fetal renal cortices, SALL4 expression was restricted to the blastema and primitive epithelium at 15 weeks' gestational age. SALL4 staining was not seen at later gestational ages, in non-neoplastic postnatal kidneys, or in nephrogenic rests.

Conclusion: Our study is the first to demonstrate SALL4 immunoreactivity in both Wilms tumor and in developing fetal kidney. Knowledge of SALL4 immunoreactivity in Wilms tumor may avoid pitfalls when considering the differential diagnosis of pediatric undifferentiated renal neoplasms. SALL4 reactivity alone should not prompt a diagnosis of renal primary or metastatic germ cell tumor. Attention should be paid to the pattern of SALL4 immunoreactivity, which is characteristically diffuse and strong in malignant germ cell tumors. Another pitfall may be SALL4 immunoreactivity in teratoid Wilms tumors, where a diagnosis of teratoma should be made only if the tumor shows a clear intent to form non-renal organs. Finally, SALL4 expression in the fetal kidney is congruent with SALL4's role in kidney development.

Abstract 3-

Diagnostic Pitfalls of Pan-Myeloid Antigen Negative Acute Megakaryoblastic Leukemia

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Background: Megakaryoblastic proliferations and acute megakaryoblastic leukemia are seen predominantly in children. Although these entities are well characterized, diagnosis can be challenging in some cases. In children acute megakaryoblastic leukemia can present with organomegaly, extramedullary involvement or lytic bone lesions, thus mimicking a metastatic solid tumor. Immunophenotypic studies are essential for correct diagnosis.

Design: Biopsies from two cases of recently diagnosed pediatric acute megakaryoblastic leukemia, and the accompanying flow cytometry (FC) and cytogenetic studies were reviewed.

Results: Both bone marrow biopsies revealed an infiltrate of blasts with associated fibrosis highlighted by reticulin stain showing marked deposition of reticulin fibers. In the first patient, an orbital mass was biopsied. FC revealed a population of CD45-, CD56+ cells that were negative for CD33, CD13, CD11b, CD15, CD14b and all other lymphoid markers tested, but did express CD61. Histologically, this lesion contained an infiltrate of atypical cells that were positive by immunohistochemistry (IHC) for CD43, CD31, CD56 and weak von Willebrand's factor and LAT. Cytogenetics demonstrated the presence of the t(1:22)(p13;q13). In the bone marrow biopsy, fibrotic foci were present which contained scattered LAT and CD31 positive large atypical cells, consistent with low-level marrow involvement.

In the second case, circulating blasts were present, and there was an infiltrate of large neoplastic cells with associated diffuse myelofibrosis. FC performed on peripheral blood revealed a CD45 dim, CD34+ blast population that weakly expressed CD56, CD117 and CD4. These cells were negative for CD33, CD13, CD11b, CD15, CD14, MPO, HLA-DR, and all other lymphoid markers tested, but did express CD61. IHC performed on the bone marrow biopsy confirmed expression of CD61 and CD43 by the blasts.

Conclusion: Acute megakaryoblastic leukemia is an uncommon form of acute myeloid leukemia which can be fraught with diagnostic pitfalls. We present two unusual cases in which the blasts were pan-negative for expression of all myeloid antigens tested other than CD61. In instances where a limited FC panels is employed, such cases could be misdiagnosed as either an undifferentiated leukemia or a non-hematopoietic neoplasm. These cases illustrate the importance of including a megakaryocytic marker in the acute leukemia flow cytometric panel for appropriate diagnosis.

Abstract 4-

Loss-Of-Function Mutations In PTPN11 Are Responsible For The Hereditary Bone Tumor Syndrome Metachondromatosis

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Background: Metachondromatosis (MC) is an autosomal dominant, incompletely penetrant combined exostosis and enchondromatosis tumor syndrome. The exostotic component, unlike osteochondroma, is more common in the digits, oriented towards the joint, and contains a cartilaginous core. The endostotic component, unlike enchondroma, occurs in the long bones as well as the digits. MC is unlinked to EXT1 and EXT2, the genes responsible for sporadic and hereditary osteochondromas.

Design: To identify the gene responsible for MC, we genotyped affected individuals from a single family segregating the disorder on Affymetrix 6.0 SNP arrays. The maximum attainable LOD score of 2.7 was observed for an 8.6 Mb interval on chromosome 12. Genotyping two smaller families corroborated the interval. A multiplexed targeted capture, using an Agilent 1M oligonucleotide array, of all exons and promoters within the interval was performed on DNAs from 16 affected individuals among 11 unrelated families. Captured DNAs were sequenced on the Illumina Genome Analyzer II and variants were analyzed using Novoalign and SAMtools.

Results: The multiplexed capture identified heterozygous mutations in PTPN11 in 4 families, including 1 nonsense and 3 frameshift mutations. Sanger sequencing of PTPN11 in remaining families revealed an additional nonsense and frameshift mutation. No mutations were detected in unaffected individuals. In total, mutations were identified in 6 of 13 unrelated families.

Conclusion: Putative loss-of-function mutations in PTPN11 were identified in MC. PTPN11 encodes SHP2, part of a family of protein tyrosine phosphatase signaling molecules. Two other disorders, Noonan and LEOPARD syndromes, are caused by heterozygous missense mutations in PTPN11 postulated to be neomorphic, antimorphic, or partial loss-of-function. We are currently testing our hypotheses that the PTPN11 mutations in MC are functionally null, and that second somatic null mutations causing complete loss of SHP2 expression are required for the development of the skeletal lesions. We speculate that somatic PTPN11 mutations might also be a cause of isolated enchondromas.

Abstract 5-

Pathology of CNS Posttransplant Lymphoproliferative Disorders: Lessons from 6 Pediatric Autopsies

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Background: Posttransplant lymphoproliferative disorder (PTLD) remains a serious condition with a poor prognosis if untreated. PTLD involving the central nervous system (CNS) in children has been rarely reported and is associated with high mortality. We report six autopsy cases of PTLD involving the CNS in children, two of which limited to CNS and unsuspected before autopsy.

Design: Autopsy records of transplant recipients were reviewed from 1996-2010 at two tertiary children's hospitals. We identified six instances of full autopsy in which the diagnosis of PTLD involving the CNS or limited to the CNS was made. The clinical course and pathology were reviewed.

Results:

Case #	Age (yrs)	Transplant type	EBV status at transplant	Time to PTLD (mos)	EBV load at PTLD diagnosis (copies/ml)	Rejection history	PTLD outside CNS	PTLD CNS
1	6	BMT	-	4	2,550,000	+	Lung, GI tract, tonsils	Cortex Basal ganglia
2	9	Lung	-	18	45,000	+	-	Cortex Cerebellum Leptomeninges
3	15	Cardiac	-	7	380,000	+	Lung, GI tract	Cortex Cerebellum Brainstem Leptomeninges
4	11	Small bowel, liver	-	8	5000	-	-	Cortex
5	13	BMT	-	5	76,000	+	Liver, GI tract	Basal ganglia
6	11	BMT	N/A	14.5	N/A	+	Kidney, adrenal, testes, lymph nodes	Cerebellum Brainstem Leptomeninges

The mean age at autopsy was 10.8 +/- 3.2 years with a mean interval to diagnosis of PTLD of 9.4 +/- 5.6 months after transplantation. Four cases were monomorphic, B cell type, EBER positive and 2 (#4, 6) were not further classified. When PTLD was confined to the brain, patients had neurologic symptoms due to multifocal brain hemorrhage. In the cases in which polymorphic PTLD was present outside the CNS, two (#3, 5) had mental status changes prompting brain biopsy demonstrating monomorphic PTLD. In one case (#5) brain lesions responded to irradiation but the patient died with disseminated extracranial disease. Most patients had documented cellular rejection except patient #4 who required low doses of FK-506. In two cases (#2, 6) atypical cells found on CSF examination were interpreted as possible PTLD but a brain biopsy was not pursued. Most patients had elevated EBV titers at the time of diagnosis. Patients with CNS only PTLD had the lowest titers.

Conclusion: Due to its rarity, pediatric CNS PTLD has not been well characterized. Since the presentation can be subtle, unsuspected and high grade, it is important to maintain a high index of suspicion and perform a brain biopsy whenever possible. In the presence of leptomeningeal involvement, the diagnosis could be made by CSF examination. In our study, most cases were multifocal and half showed leptomeningeal involvement.

Platforms - Session 2

Abstract 6-

Hirschsprung's Disease via the Lens of Proteomics

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Background: Hirschsprung's disease is a frequent congenital disorder encountered in all major children's hospitals around the world. Currently the definitive diagnosis of Hirschsprung's disease is mostly based on biopsy histology demonstrating aganglionosis and hypertrophic nerve trunks in the affected segment of bowel, sometimes correlated with increased

Acetylcholinesterase (AChE) in aganglionic segment. No unique biomarker is available yet.

Design: Single Hirschsprung's disease pull-through sample provided the proper material for this exploratory study. Representative samples taken from -80 degree Celsius frozen aganglionic, transitional and normal ganglionic segments were utilized in quantitative mass spectrometry (LC-MS/MS). It was conducted with Thermo-Finnigan linear ion-trap (LTQ) mass spectrometer coupled with a Surveyor autosampler and MS HPLC system (Thermo-Finnigan) with digested sampled. The acquired data were searched against the International Protein Index (IPI) human database (ipi.HUMAN.v3.37) using SEQUEST (v. 28 rev. 12) algorithms in Bioworks (v. 3.3). The searched peptides and proteins were validated by PeptideProphet and ProteinProphet in the Trans-Proteomic Pipeline (TPP, v. 3.3.0) A quantitative analysis of proteins' relative abundances was performed using spectral counting of peptides, whose data were from TPP. Significant difference analysis was completed with t-test in Microsoft Excel.

Results: 1869 proteins have been identified. Among them, 1702 proteins have been quantified. Striking protein expression difference between aganglionic segment and ganglionic segment have been identified.

Table: Aganglionic segment at 4 cm vs. ganglionic segment at 18 cm. The numbers are folds change. The transitional segment at 14 cm has similar protein expression pattern as ganglionic segment at 18 cm (date not shown).

Molecules	Up-regulated	Molecules	Down-regulated
DOCK8	45.11	GFPT2	-7.774
RPL30	12.165	GFPT1	-7.774
PHB	9.856	TPM2	-7.276
PARK7	8.325	AHSG	-4.921
IGK	6.852	RPS14	-4.459
RAB11A	3.204	GOT2	-4.321
TST	3.154	PGM5	-4.15
SDHA	3.05	TPM1	-4.057
		TNC	-3.832
		PEBP1	-3.463

Conclusion: Dramatic different protein expression patterns have been discovered as we predicted. These new markers candidates will be correlated with new study cases by immunohistochemistry studies and under scrutiny for potentially useful markers. Potentially some of the markers will be useful as ancillary diagnostic tools for Hirschsprung's disease as well as its related entities such hypoganglionosis, intestinal neuronal dysplasia and chronic idiopathic intestinal pseudo-obstruction or severe constipation in general.

Abstract 7-

Nestin in Peripheral Nerve Sheath Tumors: a Marker of Tumor Progression?

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Background: Nestin, an intermediate filament protein, is expressed in neuroectodermal progenitor and stem cells, as well as in tumors of neuroectodermal lineage and correlates with histologic grade in several neoplasms. Although nestin expression has been reported in nerve sheath tumors, its correlation with their histologic grade is unknown. Also, loss of the product of the tumor suppressor gene INI-1 has been reported in NF2 associated Schwannomas, but not in sporadic and NF1 associated nerve sheath tumors. In this study we evaluate and correlate nestin expression in nerve sheath tumors of various histologic grades from patients with and without NF1.

Design: Twenty four nerve sheath tumors from our institution, 14 neurofibromas, 4 of which atypical, 1 low grade MPNST and 9 high grade MPNST were stained for nestin and INI-1. Sixteen tumors occurred in patients with NF1 and 11 were sporadic. Eleven of the NF1 associated tumors were neurofibroma/low grade MPNST and 4 were high grade. Percentages of nestin positive tumor cells were correlated with histologic grading. Also, nestin expression was correlated with NF1 status in the high grade MPNST group. Statistical analysis was performed with the t-test.

Results: High grade MPNST expressed more than 70% nestin positive cells. Three of the atypical neurofibromas (all in patients with NF1) had 30% to 60% positive cells, in contrast to the single sporadic atypical neurofibroma (10% positive cells). Most neurofibromas without atypia were nestin negative. Two cases expressing 20% and 40% positive cells showed high uptake by positron emission tomography (PET). In general, focal pattern of staining was observed in tumors with low nestin expression, multifocal in grade 2 tumors and diffuse in grade 3 tumors. Overall, there was a statistically significant difference of nestin expression in high grade MPNST when compared to atypical neurofibroma and low grade MPNST ($p=0.003$). Furthermore, high grade MPNST tended to have higher nestin expression in NF1 patients ($p=0.039$).

Conclusions: Our data show that nestin expression in nerve sheath tumors correlates with histologic tumor grade and NF1 status and suggest a role for nestin in their progression.

Abstract 8-

Seven Cases of Colorectal Adenocarcinoma in Children with Diverse Pathological Subtypes and MSH Gene Abnormalities

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Background: Colorectal adenocarcinoma is exceedingly rare in the pediatric population (1 per 5-10 million children) and may be sporadic or familial. Multiple histological subtypes have been identified, including conventional adenocarcinoma, mucinous adenocarcinoma, and signet ring adenocarcinoma. Strong associations between adenocarcinoma and germline mutations in DNA mismatch repair genes (e.g., MLH1, MSH2, MSH6) have been established, especially in hereditary colorectal cancer syndromes such as Lynch syndrome. Additionally, reduced expression of E-cadherin has been associated with aggressive metastases and poor prognosis in adult colorectal adenocarcinomas; however, its role in predicting prognoses in pediatric cases remains unclear.

Design: Seven patients with primary colorectal adenocarcinoma were retrieved from our archive. Case histories, pathology reports, and clinical summaries were reviewed. E-cadherin immunostains were performed in five of the seven cases, and available molecular-genetic test results were evaluated.

Results: The seven patients included six males and one female with an age range of 15-19 years (mean 16 years) at diagnosis. Tumor histologies included conventional adenocarcinoma (n=2), mucinous adenocarcinoma (n=3), and signet ring adenocarcinoma (n=2). Sites included the transverse colon (n=2), splenic flexure (n=1), descending colon (n=1), rectosigmoid (n=1), and rectum (n=2). Subsequent metastases were identified in five patients. In cases stained for E-cadherin, two were strongly positive and three were weakly positive; there was no correlation with tumor metastasis or prognosis. Additionally, three patients had family histories of carcinoma and were tested for Lynch syndrome. Two patients (28%) were positive: one male patient had a deletion of nucleotide 20 in MSH2, and the female patient demonstrated biallelic MSH6 mutations. Results for the third patient were negative.

Conclusion: Mutations in MLH1, MSH2, and MSH6 have been reported in more than 95% of familial colorectal adenocarcinomas and represent an important diagnostic marker for this disease entity. Overall, nearly 30% of colorectal carcinomas are familial with an identifiable genetic basis, which is consistent with our study results. E-cadherin showed no prognostic significance in this pediatric population. Our findings highlight the importance of genetic testing in children with colorectal cancer.

Abstract 9-

Cervical Ribs Are More Prevalent in Stillborn Fetuses than in Liveborn Infants and Are Strongly Associated with Fetal Aneuploidy

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Background: European population studies have reported an increased prevalence of cervical ribs in patients with childhood cancer as well as in stillborn fetuses. Cervical ribs are part of the phenotypic spectrum in aneuploidy. There are a few reports of familial cases of isolated cervical rib with autosomal dominant inheritance. The objectives of our study were to determine the prevalence of cervical ribs in stillborn fetuses undergoing autopsy at our institution and to search for significant associations with cervical ribs.

Design: Data from autopsies performed at Primary Children's Medical Center, Utah between 2006 and 2009 on 225 stillborns (≥ 20 weeks) and 93 liveborn infants (< 1 year) were reviewed. Digital fetal radiographs in anterior-posterior and lateral views were taken for each of those autopsies and analyzed using the IMPAX AGFA software version 6.3.1. Chi-square analysis and general linear models were used for statistical analysis of the data.

Results: The overall prevalence of cervical ribs was higher in stillborns than in liveborn controls (43.1% vs 11.8%). Karyotypes were available on 93 (41.3%) of the stillborns. Of those, cervical ribs were present in 33 of 76 (43.4%) stillborns with normal karyotype, and in 13 of 17 (76.4%) stillborns with aneuploidy. Specifically, we found cervical ribs in 4 of 5 fetuses with Monosomy X; 4 of 7 with Trisomy 21; 2 of 2 with Trisomy 13 and 1 of 1 with Trisomy 18. Females with unavailable karyotypes were far more likely to have cervical ribs than those with normal karyotypes ($p = 0.0002$). This greater likelihood was not observed for males. We hypothesize that this effect may be due to unsuspected Monosomy X among some of the female fetuses. Among the stillborns with normal karyotypes, we found no significant association with gender or gestational age at fetal death. We also did not find any specific malformation that showed a statistically significant association with the presence of cervical ribs. However, we did identify a pair of stillborn sisters, both of whom had cervical ribs, IUGR and long hypercoiled umbilical cords after oligohydramnios.

Conclusion: Our findings concur with previous studies reporting a high prevalence of cervical ribs among stillborns. The results also support the hypothesis that cervical ribs are markers for a variety of disadvantageous developmental events occurring during organogenesis, and have been subject to strong negative selection during evolution.

Abstract 10-

The Need To Sub-Classify Syncytial Knots: Wave-Like Syncytial Knotting In Distal Villous Hypoplasia

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Background: A recent description of syncytial knots classifies knots based on the presence of apoptotic or necrotic features and on knot shape and size (1). This classification is not widely used and its utility in diagnostic practice is untested. One of the described forms of knotting, “wave-like knots” was described in scanning electron microscopy of villi as a repeating pattern of syncytial ridges. Although the nuclei in wave-like knots showed apoptotic features, the basis of the unusual ridge pattern was unknown. We sought to test the applicability of this classification in a group of patients with severe placental disease with putative trophoblast dysfunction (as evidenced by abnormal maternal β -HCG or inhibin levels).

Design: 12 placentas from pregnancies ending prior to 28 weeks were identified from the records of the placenta clinic at Mount Sinai Hospital and were compared with 24 controls. Cases had either a β -hCG \geq or = 3.0 MoM or an Inhibin \geq or = 3.0 MoM in results from second trimester maternal serum screening. Syncytial knots were categorized as knots due to tangential sectioning (TS), wave-like knots (WK), giant knots (GK) and other (OK). Patterns of trophoblast necrosis or aponecrosis were documented.

Results: Extensive or regional distal villous hypoplasia (DVH) was present in 8 of 12 cases versus 0 of 24 controls ($p = 0.001$). WK were present in 7 of these 8 cases. The 8th case of DVH had a different trophoblast morphology, with extensive aponecrotic change in the trophoblast. A previously unrecognized linear arrangement of syncytial nuclei was identified in both pathological and normal placentas. GK were seen in 3 cases and 1 control placenta, while an increase in knots due to TS was seen in 1 case and in 0 control placentas.

Conclusion: By sub-characterizing syncytial knotting we demonstrated an association between DVH and WK in our study group. Based on our identification of linear nuclear arrangements in normal trophoblast we propose that WK result from accumulation of increasingly senescent nuclei along inherent lines of syncytial organization. Such accumulations would eventually produce the ridges that define the wave-like knot. By demonstrating that there is an association between WK and DVH we have linked specific trophoblastic morphological changes, suggestive of alterations in trophoblast turnover, to a particular form of villous maldevelopment. This provides an important insight into the pathogenesis of DVH.

(1) Kauffman P, Huppertz B (2007) Tenney-Parker changes and apoptotic versus necrotic shedding of trophoblast in normal pregnancy and pre-eclampsia. In Lyall F, Belfort M (Eds.). Pre-eclampsia: Etiology and Clinical Practice. New York. Cambridge University Press.

Platforms - Session 3

Abstract 11-

LAIR2-Positive Extravillous Trophoblast Migrate to the Implantation Site and Invade Maternal Decidual Vessels

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Background: Leukocyte-associated immunoglobulin-like receptor 2 (LAIR2) was identified on a global gene expression microarray analysis of surplus chorionic villus sampling (CVS) tissues as down-regulated in the first trimester of preeclampsia pregnancies. LAIR2 is the soluble receptor counterpart to LAIR1, an inhibitory receptor shown to bind collagen. In situ and immunohistochemical studies have previously shown that LAIR2 expression is highly restricted, confined to the more distal portions of extravillous trophoblast (EVT) cell columns. This study extends the analysis of LAIR2 localization to include the placental implantation site and maternal decidual vessels.

Design: IHC was performed on FFPE samples of first trimester placentas. Localization and intensity of staining were determined.

Results: Immunohistochemical staining detected intracellular LAIR2 staining throughout the implantation site. Intracellular LAIR2 was found only in extravillous trophoblast. This trophoblast included the invasive EVT infiltrating the maternal decidual vessels and the EVT forming the endovascular trophoblastic plugs. Extracellular staining of this soluble receptor was also found on the endothelial surface of maternal decidual vessels and throughout the acellular material within the implantation site.

Conclusion: IHC staining for LAIR2 detected specific, highly localized expression within the placental implantation site. This expression was particularly prominent within the endovascular EVT and the EVT forming endovascular trophoblastic plugs. We hypothesize that this soluble receptor plays an important role in trophoblast invasion. Based on the microarray data and the localization, decreased expression of LAIR2 may play an etiologic role in preeclampsia by preventing the normal endovascular invasion and remodeling of maternal decidual vessels.

Abstract 12-

Altered Serotonin Uptake Transporter Expression in Patients with Pregnancy Induced Hypertension.

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Background: The intrauterine environment is characterized by high catecholamine secretion and clearance. This clearance is mediated in large measure by placental transport proteins. Alterations in the function or capacity of this transport system are likely to have significant effects on the developing fetus. Pregnant illicit drug abusers (especially cocaine, CO), selective serotonin reuptake inhibitor (SSRIs) users, and a number of mothers with pregnancy induced hypertension (PIH) have all elevated serum serotonin levels thus the term hyperserotonemic disorders (HD). Serotonin uptake transporter (SERT) of cytotrophoblasts has been shown to control serotonin level in the placenta. We hypothesized that altered SERT expression may contribute to pregnancy related hyperserotonemic disorders.

Design: 16 normal placentas representing mid and term gestational age were used to determine normal SERT expression pattern. In addition 10 CO, 11 SSRIs and 20 PIH placentas were collected. Slides were stained with SERT antibody. Quantitative morphometric immunostain analysis was done by using Nuance VIS-FL Multispectral Imaging System. The percentage of positive stained area with cells showing DAB positive membrane/cytoplasmic positivity/100 high power fields was acquired and compared between the two trimesters of gestation (control group) and PIH, SSRI and CO placentas. For the statistical analysis, Mann-Whitney, Kruskal-Wallis, and analysis of variance tests were performed.

Results: Predominantly membranous SERT staining was seen in the villous/extra villous cytotrophoblasts and the expression showed a slight increase towards the end of the gestation. PIH placentas (4.2%) had similar SERT expression to that of controls (4.1%), but significantly higher when compared to that of CO (2.3%) and SSRIs placentas (2.1%). When the groups were matched for gestational age with the controls (3.7%) the CO placentas (3.5%) and the SSRIs (2.4%) placentas showed significantly decreased SERT expression ($p=0.001$). The lowest expression was observed in the SSRIs group when compared with controls ($p<0.05$).

Conclusion: As far as we know there are no published studies which were designed to compare the immunohistochemical profile of these biogenic amines and their transporters in placentas from fetus exposed to cocaine, SSRIs or hypertension during pregnancy. SERT expression is decreased in cocaine and anti-depressant users which can be the primary cause of the elevation in the serotonin levels observed in these patients. SERT expression was not altered in PIH. It is possible that other catabolic component of serotonin metabolism (i.e monoamine oxidase) is altered, which might explain the high serotonin levels in these select patients.

Abstract 13-

Pale Avascular Villi Provide Insights Into The Pathogenesis of Placental Fibrinoid Deposition

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Background: Avascular villi are important markers of placental or fetal disease. We sought to determine the frequency of avascular villi in a group of placentas with clinically severe placental disease, to determine if such avascular villi could be sub-categorized and to see if such sub-categories were clinically significant.

Design: 12 placentas from pregnancies ending prior to 28 weeks as a result of placental disease were identified from the records of the placenta clinic at MSH and were compared with 24 controls. Morphological variants of avascular villi were categorized in routine H/E sections using stromal staining characteristics, trophoblast nuclear and cytoplasmic/syncytioplasmic features and associated findings.

Results: Avascular villi were found to fall into 3 groups, 1) avascular villous clusters suggestive of chronic fetal vascular obstruction, 2) an apparent end point in distal villous hypoplasia and 3) pale avascular villi (PAV) with myxoid stroma and associated perivillous fibrinoid. The earliest myxoid stromal alterations of PAV were seen in villi that also showed syncytiotrophoblast degeneration with fibrin type fibrinoid deposition between the syncytiotrophoblast and the underlying cytotrophoblast. The latter showed morphological changes that indicated a switch to an extravillous trophoblast (EVT) phenotype. This switch in phenotype was confirmed in selected cases by demonstrating immunohistochemical positivity for HLA-G. In more advanced lesions, the villous stroma was essentially replaced by myxoid material and the newly formed EVT lost its position next to the basal lamina as matrix type fibrinoid material increased. These PAV were seen singly or in small clusters in all control placentas but their numbers increased and aggregates became larger as perivillous fibrinoid increased.

Conclusion: We have identified a type of avascular villous that is the result of a specific form of trophoblast and villous degeneration that we term a pale avascular villous. A key step in this degenerative process is the switching of villous cytotrophoblast to an EVT phenotype. Such EVT is capable of secreting matrix type fibrinoid in a non-polar manner, thus separating itself from its native villous basal lamina to become the EVT typically seen in pathological fibrinoid deposits. Fibrinoid formed in this manner may therefore be largely unrelated to any pro-thrombotic tendency and may instead be a marker of whatever triggered the associated villous degeneration. We suggest that the inciting event is trophoblast injury and that different immune or non-immune mechanisms may act via this common morphological pathway to produce increased perivillous fibrinoid.

Abstract 14-

Immunohistochemical Study of Vascular Architecture and Mib-1 Proliferation Index in Early Spontaneous Miscarriages

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Background: The majority of spontaneous abortions of the first trimester are due to numerical chromosomal abnormalities.

Design: 118 early miscarriages were analysed considering histological features of the villi on HE staining. Stromal vasculogenesis was studied by antigen CD31 for the vascular architecture and GLUT-1 to identify immature vascular cells. Protein p57 was used to differentiate between complete and partial molar pregnancies and MIB-1 to evaluate the villous proliferation index. On all placental paraffin embedded-tissues, FISH was performed with probes for chromosomes 13, 18, 21, 16, 22, X, Y. Aneuploidy was further confirmed with DNA index on the same sections.

Results: FISH analysis revealed 46 aneuploidy (38.6%), and 73 cases were euploid (33 XX and 40 XY). The numerical chromosomal abnormalities were the following: trisomy 13, monosomy 16 and monosomy 21 (1 case of each, 2.2%), tetraploidy (2 cases; 4.4%), trisomy 18 and 21 (3 cases of each, 6.5%), trisomy 16 (5 cases, 10.9%), triploidy (9 cases, 19.6%; 7 with XXY, 2 XXX) monosomy X (10 cases, 21.7%), trisomy 22 (11 cases, 23.9%). DNA index analysis confirmed all the aneuploidies.

Compared to euploid cases, triploidy, tetraploidy, trisomy and monosomy X cases showed the typical histological and vascular features commonly described in literature. Monosomy 16 and 21 revealed not specific morphology apart from few hydropic villi with less developed vasculature. CD31 revealed a well developed vasculature with stromal branching in trisomy 22 and monosomy X. The vasculature was less developed in trisomy 21 and 16 and irregular in trisomy 18. More immature and isolated vascular cells (GLUT-1 positive) were found in triploidy, tetraploidy, trisomy 22, and monosomy X, while in trisomy 16 they were scattered. MIB-1 was increased in the cytotrophoblast layer and in the stroma in trisomy 22, while in tetraploidy, triploidy, trisomy 16 and 21 it was significantly reduced. MIB-1 was not significant in trisomy 18 and monosomy X. We did not study the single cases (monosomy 16, 21 and trisomy 13).

Conclusion: Predictions of karyotype from histological examination only should be avoided but associated with FISH and DNA index analysis. However, if not available, variations in villous vasculature, vessels maturation and MIB-1 index, may give a further suspicion of abnormal karyotype.

Abstract 15-

Maternal Serum C-Reactive Protein In The Second And Third Trimester: Correlations With Placental Inflammation At Delivery

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Background: C-reactive protein (CRP), an acute phase protein produced by the liver in response to pro-inflammatory cytokines, is a useful biomarker for systemic inflammation. Elevated maternal CRP levels have been associated with adverse pregnancy outcomes such as preterm birth and preeclampsia. However, placental histologic correlates with elevated second and third trimester maternal CRP levels have not been well studied. The objective of this study was to assess maternal CRP in the second and early third trimester and correlate the findings with histological evidence of placental inflammation.

Design: African-American and Caucasian pregnant women from two prenatal clinics at Northwestern Memorial Hospital were recruited between May 2008 and July 2009. Two blood samples were collected, one in the second trimester between 14 and 22 weeks and the second in the third trimester between 28 and 32 weeks. Samples were analyzed for serum CRP using a high-sensitivity standard enzyme immunoassay. The quantity of CRP in each sample was determined based on comparison with calibrator values. Placentas were collected at the time of delivery, grossed and sectioned by standard methods. H&E sections of the membranes, umbilical cord, chorionic plate and chorionic vessels were evaluated for the stage and grade of acute inflammation. The presence of chronic inflammation, specifically chronic villitis, chronic deciduitis with or without plasma cells, chronic decidual perivasculitis, and chronic chorioamnionitis was recorded. Statistical analyses were performed using SPSS.

Results: 114 women were recruited, 58 Caucasian (28 medicaid and 30 private insurance) and 56 African-American (30 medicaid and 26 private insurance). Mean maternal CRP in the second and third trimester was significantly higher in patients with chronic villitis in the placenta (2nd trimester: 16.8 ± 4.25 vs. 8.95 ± 1.13 , $p=0.017$; 3rd trimester: 18.27 ± 4.49 vs. 8.44 ± 1.37 , $p=0.01$). Patients with CRP levels in the top quartile were significantly more likely to show any chronic inflammatory lesion in the placenta (40% vs. 18%, $p=0.04$), and chronic villitis (30% vs. 10%, $p=0.03$) than those in the lower quartiles. In addition, patients with CRP levels in the top tertile were more likely to show chronic deciduitis (28% vs. 10%, $p=0.04$). Acute placental inflammation was not significantly associated with CRP levels.

Conclusion: Maternal CRP levels are elevated in the second and third trimester in women whose placentas show chronic inflammation at the time of delivery. This pilot data suggests chronic placental inflammation is associated with a more systemic maternal inflammatory response. The cause-effect relationship deserves further study.

Abstract 16-

Correlation Between Cerebral and Placental Damage in Fetuses Congenitally Infected by Cytomegalovirus

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Background: Congenital cytomegalovirus (CMV) infection is a major cause of central nervous system damage leading to sensorineural hearing loss, mental retardation and cerebral palsy.

Design: This work aimed to study the pathogenesis of cerebral damage in 27 aborted fetuses with CMV infection. Fetal CMV infection was documented at 20-21 weeks gestation by invasive prenatal diagnosis (amniotic fluid with a viral load $>10^5$ GE/ml). CMV early (ppUL44) antigen expression, inflammatory response (antigen CD45, CD3, CD4, CD8, CD20, granzyme B) and apoptosis (Cleaved Caspase-3) were studied in all fetal tissues using immunohistochemical staining procedures. The CMV viral load in paraffin embedded tissues was detected by Real Time-PCR.

Results: No histological damage was observed in 12 CMV-negative brains. Six out of 15 CMV-positive brains showed scattered inflammatory cells without tissue damage. In 4 CMV-positive brains an immuno-mediated cerebral tissue damage with multifocal aggregates of activated CD8 T lymphocytes in the areas with CMV-positive cells was observed. Caspase-3 positive cells undergoing apoptosis were often located in close proximity of activated cytotoxic lymphocytes. In 5 CMV-positive brains the tissue necrosis was more frequently associated with inflammatory, apoptotic and CMV positive cells (immuno-mediated damage), although necrotic areas without viral inclusions were also observed suggesting hypoxic injury. In fact, the majority of placental villi in the corresponding 5 placentas were necrotic or hydropic causing a severe placental dysfunction. The tissue CMV viral load was higher in fetuses with severe brain damage than fetuses with mild cerebral damage.

Conclusion: Brain damage may be due to a direct effect of the CMV (cytopathic damage) and to indirect effects such as CD8 T cytotoxicity triggered by infected cells and hypoxia due to severe placentitis. In fact, high viral load in the placenta is related to a severe inflammatory infiltrate with necrosis reducing its capacity to provide oxygen to the developing fetus.

Posters

Abstract 17-

Prenatally Diagnosed Stricture and Aneurysm of Ductus Arteriosus as a Cause of Fetal Hydrops and Death

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Background: Fetal ductus arteriosus aneurysms (DAA) can occur in association with maternal diabetes mellitus, systemic lupus erythematosus, connective tissue disorders, Smith-Lemli-Opitz syndrome, and some trisomies. Neonatal DAA is not uncommon (8%). Potential complications include thromboembolism, rupture, and death. Neonatal cases can resolve spontaneously after birth or, rarely, require surgical intervention. Fetal DAA can be diagnosed antenatally by sonography, usually in the third trimester

Design: This is a case report of a fetus of a diabetic and obese mother in whom fetal echocardiography at 23 weeks gestation revealed constriction of the ductus arteriosus with aneurysmal dilatation of both main pulmonary artery and ductus. In addition, right ventricular failure associated with pulmonary and tricuspid regurgitation, right ventricular hypertrophy, and severe pulmonary artery and right ventricular hypertension was observed. At 26 weeks, a lobular mediastinal mass and features of fetal hydrops were revealed by MRI. The mother developed mirror syndrome with elevated liver function tests and a borderline urinary output. In utero fetal demise occurred a few days later.

Results: At autopsy, the hydropic fetus showed a massively dilated right heart and hepatomegaly. The mass-like, massively enlarged, dumbbell-shaped, tortuous, and focally obliterated ductus arteriosus straddled the aorta and protruded into the left mediastinum and posterior to the aorta. Microscopically, the ductus showed abnormal intimal cushions and defective elastin fibers. The pulmonary artery showed mucoid degeneration of the media and extensive mural thrombi, focally calcified, focally occlusive, and extending bilaterally into its pulmonary branches. There were features of pulmonary hypertension. The 586gm placenta was hydropic, with hypocoiled umbilical cord with a chorda.

Conclusion: This case of a large DAA is unusual as it was diagnosed in mid second trimester, was complicated with stricture and massive occlusive thrombosis, extending into the pulmonary artery branches. This raises a possibility of an underlying connective tissue disorder. Early development of fetal hydrops, before fetal viability, was the cause of poor outcome in this case and prevented any successful therapeutic intervention. Documentation of natural outcome in early severe cases of DAA, like ours, should facilitate the development of a more successful management in the future.

Abstract 18-

Comparative Evaluation Of Specimen Collection Methods For Ultrastructural Diagnosis Of Primary Ciliary Dyskinesia Syndrome

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Background: Electron microscopic study of respiratory mucosa remains the “gold standard” technique for establishing a diagnosis of primary ciliary dyskinesia syndrome, and the variability in its success is largely dependent upon the obtainment of a satisfactory tissue sample. The objective of this study was to assess the comparative efficacy of commonly used specimen collection methods and to provide recommendations on how best to proceed with this aspect of the diagnostic workup.

Design: A generically representative sample consisting of 100 consecutively received specimens of respiratory mucosa, submitted by an undetermined number of investigators from 12 institutions using a variety of self-selected collection methods, was comparatively evaluated for testing adequacy.

Results: Overall, 67 of the specimens proved fully evaluable (of which, 5 exhibited significant abnormalities), 16 were marginally evaluable, and 17 not evaluable. The curette technique produced the highest overall rate of success in generating good/excellent results (75%, n=20), followed by forceps (71%, n=7), brush (48%, n=60), and blade (46%, n=13). The nose proved to be a more reliable biopsy site (60%, n=72) than the trachea (42%, n=24). With nasal specimens, curettage (75%, n=20) was more often successful than brushing (55%, n=45). With tracheal specimens, forceps (70%, n=10) were more often successful than brushings (21%, n=14).

Conclusion: With consideration given also to other factors (e.g., relative expense, ease, skill required, patient comfort and safety), it therefore is recommended that a diagnostic study be initiated using a nasal specimen obtained by curettage. If any morphologically normal cilia are observed, the workup can be discontinued. If a consistent potentially significant abnormality is observed, confirm the diagnosis with a followup study of nasal mucosa (obtained by curettage) to demonstrate its permanence and a concomitant study of tracheal mucosa (obtained by forceps) to demonstrate its universality.

Abstract 19-

Hyalinizing Spindle Cell Tumor with Giant Rosettes Presenting as a Tongue Mass in a 10 year old.

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Background: Hyalinizing spindle cell tumor with giant rosettes (HSCT) is generally regarded as a variant of low-grade fibromyxoid sarcoma, sharing a common cytogenetic translocation t(7;16)(q34;p11). The majority of cases occur within the trunk and deep soft tissue of the extremities. Rare cases have been reported in the orbit, omentum, small bowel, broad ligament, neck, axilla, parapharyngeal and presacral regions. To our knowledge, this is the first reported case of HSCT involving the tongue.

Design: We report a case of a 10-year old female presenting with a progressively expanding mass of the lateral tongue.

Results: The patient is previously healthy female with a four-month history of an enlarging, painless mass involving the lateral tongue. There is no history of trauma to the area. She experienced progressive difficulty articulating and swallowing. A CT scan demonstrated a large solid mass in the sublingual space, approximately 4.3 x 2.7 cm, displacing the sublingual and submandibular glands, likely related to the intrinsic muscles of the tongue. The mass was surgically excised. Grossly, the cut surface was dense, white, and whorled with focal yellow flecks. Microscopically, the mass was thinly encapsulated and composed of bland spindled cells, with varying degrees of cellularity, situated within a densely hyalinized stroma. Focal areas of myxoid cystic degeneration were present. There was no significant cytologic atypia or mitotic activity. Scattered large rosette structures, composed of central collagenous cores surrounded by a mantle of densely cellular spindle cells, were present. The spindle cells at the periphery of the collagenous core were positive for vimentin and negative for desmin, smooth muscle actin, S-100 protein, CD 34, ALK and epithelial membrane antigen.

Conclusion: HSCT is a rare tumor that is generally regarded as a variant of low-grade fibromyxoid sarcoma. Most patients are in their third or fourth decade of life and present with a deep-seated mass involving the extremities. Although it has been reported to arise in a host of rare and unusual sites, this entity has not been previously described in the tongue. Although HSCT has a deceptively bland appearance, recurrence and metastasis may occur. Wide and complete surgical excision is recommended. Although primary sarcomas of the tongue are rare, they are well documented. HSCT must also be considered in the differential diagnosis of spindled tumors involving the oral cavity.

Abstract 20-

Hepatic Pulmonary Fusion in 2 Patients with Diaphragmatic Hernia and a Third Patient with Pentalogy of Cantrell

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Background: Hepatic pulmonary fusion is a rare lesion characterized by a fibrous connection or true interspersed of liver and lung tissue. The cause of hepatic pulmonary fusion remains unknown. During the first six weeks of gestation, the liver, lungs and diaphragm form in close continuity, and it is possible that failure of the diaphragmatic membranes to fuse permits the fusion of adjacent pulmonary and hepatic tissue anlagen.

Design: Cases of hepatic pulmonary fusion were retrieved from the files of Children's Healthcare of Atlanta at Egleston from 2005 to 2009. Clinical, pathological, and autopsy findings were evaluated for each case. Tissue obtained during the surgical hernia repair was examined.

Results: Three cases of hepatic pulmonary fusion were identified. All cases were associated with diaphragmatic hernia. A six-year-old female and an eight-month-old male were diagnosed with diaphragmatic hernia, and hepatic pulmonary fusion was subsequently identified during surgical repair of the hernia during which separation and/or resection of the fused parts were performed; both patients are doing well today. The third case was a Pentalogy of Cantrell newborn female who expired shortly after birth. An autopsy revealed complete agenesis of the diaphragmatic leaflets with the majority of the liver situated in the right hemithorax. Finger-like projections of liver tissue were also identified surrounding and firmly adhered to the right lower lobe lung parenchyma. Additionally, the infant showed ectopia cordis, defective lower sternum, and a large omphalocele containing portions of liver and small and large bowel.

Conclusions: Here, we present three new cases of hepatic pulmonary fusion, including a case of Pentalogy of Cantrell. Although the molecular-genetic basis is unknown, it has been proposed that this anomaly is secondary to developmental failure of the mesoderm between days 14-18 after conception. Since there are no cases of hepatic pulmonary fusion reported in the absence of diaphragmatic hernia, the authors believe that this phenomenon is purely attributed to the diaphragmatic maldevelopment. Therefore, understanding the molecular-genetic basis of the diaphragmatic hernia may shed some light on this unusual presentation and explain why many other cases of diaphragmatic hernia show no such fusion.

Abstract 21-

Basal Plate Plaque: An Organizing Placental Thrombotic Process

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Background: Placental intervillous thrombi are not known to undergo organization, in contrast to thrombi or hematomas elsewhere. As a result, reactive intervillous spindle cell proliferations are essentially unknown in the placenta. We identified a spindle cell proliferation at the basal plate of a placenta from a fetus showing severe intrauterine growth restriction at 20 weeks gestational age. Our aim was to clarify the nature of this previously undescribed process.

Design: The details of the case including the results of specialist placental clinical evaluation were collated. Immunohistochemistry for cytokeratin AE1/AE3, smooth muscle actin, desmin, CD68 and vimentin was used to identify the nature of the lesion's spindle cells. As the fetus was male, interphase fluorescence in-situ hybridization (FISH) was performed to determine whether the lesion's spindle cell population was maternal or fetal, using a Vysis AneuVysion assay kit provided by Abbott Molecular.

Results: The pregnancy was interrupted at 20 weeks gestational age due to the severity of the fetal growth restriction. Maternal serum screening results showed a β -hCG of 22.17 MoM, an Inhibin of 5.17 MoM, an AFP of 1.24 MoM and a PAPP-A of 0.05 MoM. At 18 weeks gestational age, the placenta was noted to have an abnormal sonographic texture but uterine artery and umbilical artery dopplers were normal. Pathologically there was distal villous hypoplasia with prominent necrotic and aponecrotic degeneration of trophoblast. The spindle cell proliferation was located on the villous aspect of the basal plate in multiple slides and measured up to 0.8mm in thickness. It formed an irregular, multifocal plaque with smooth muscle actin positive and cytokeratin negative spindle cells set in a loose stroma containing scattered inflammatory cells. In areas, the periphery of the plaque was continuous with a thin layer of thrombus. FISH identified the lesional cells as being female and thus of maternal origin.

Conclusion: A basal plate plaque is composed of maternal spindle cells with a myofibroblast phenotype. It appears to originate through organization of thrombus deposited at the basal plate, a unique phenomenon for the placenta. There was associated severe placental disease, as evidenced by the associated pathology, the fetal growth restriction and the significant abnormalities in maternal serum markers. Although the lesion may form as a secondary phenomenon, it may in itself have the potential to impair flow in a manner analogous that suspected in maternal floor infarction. Having since identified other, more limited examples of this process, we suggest that the lesion deserves further study so that its clinical and functional significance can be elucidated.

Abstract 22-

A Case of Spontaneous Human Superfetation

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Background: In normal pregnancies, a complex interplay of hormones prevents additional cycles of ovulation and implantation of a second embryo. Superfetation, otherwise known as 'conception during pregnancy', is such a rare occurrence in humans that its very existence has been debated. Most published examples have been diagnosed late in gestation, when superfetation is difficult to distinguish from twinning with severe intrauterine growth restriction of one fetus. Fewer than a dozen cases of human superfetation have been reported with supporting sonographic and/or laboratory data, and in most cases assisted reproductive technology has been implicated. We report an early second trimester example of spontaneous human superfetation with an estimated 7-week discrepancy in gestational age.

The patient was a 22 year-old pregnant G3P2 woman who elected termination of pregnancy at a presumed post-conception age of 14 weeks. Dilation and curettage was performed.

Design: Gross examination of the curettages revealed a fragmented fetus and intact embryo. Measurements and anatomical features of each were correlated with developmental norms. DNA was extracted from maternal decidua, and each fetus. Short tandem-repeat (STR) analysis (using the AmpFISTR® Profiler Plus™ kit) was performed to confirm a common maternal origin and exclude the possibility of intermixed specimens.

Results: The fragmented fetus had a foot-length of 2.2 cm. While fragmentation precluded detailed examination of all structures, numerous anatomic features and measurements were consistent with a developmental age of 14 weeks. The non-dysmorphic embryo (crown-rump length = 1.7 cm) was intact, not autolyzed, and attached to an immature placenta. STR analysis of 9 allele pairs revealed that the fetal samples each shared an allele per pair with the maternal sample, consistent with the fact that the fetuses are siblings. Also, the fetal samples were discordant at multiple alleles, which rules out the possibility of monozygotic twins with severe growth discordance.

Conclusion: In this case the patient apparently conceived the second embryo 7 weeks after conception of the first fetus. To our knowledge, this is the longest reported interval between implantation of the first and second embryos. Superfetation is a rare cause of twin pregnancy that may be mistaken for discordant growth restriction, particularly late in gestation.

Abstract 23-

Fibrocartilaginous Mesenchymoma, an Aggressive Benign Tumor which can be Mistaken for Other Malignant Bone Tumors: A Case Report & Review of the Literature

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Background: Fibrocartilaginous mesenchymoma (FCM) is a rare osseous tumor that primarily arises in the long bones of children and young adults. To date, only 21 cases have been reported. This lesion can grow quickly and reach a considerable size, despite its benign nature. Local recurrence has been reported in cases of incomplete excision. Pathological diagnosis of FCM have proven challenging and can be mistaken for a spectrum of benign and malignant bone tumors, including desmoplastic fibroma, fibrous dysplasia with cartilaginous differentiation, dedifferentiated chondrosarcoma, and low grade osteosarcoma. Histologically, FCM displays unique epiphyseal plate-like cartilage with destruction of the surrounding cortical bone and exhibits dense fibrous stroma mimicking desmoplastic fibroma.

Design: We examined an unusual case of FCM in a patient at Children's Healthcare of Atlanta. All clinical, radiological, and pathological findings were reviewed.

Results: An eleven-year-old male presented with a left proximal humerus mass thought to be a simple bone cyst. The mass grew slowly over three years; however, two months before he sought medical attention, the mass grew rapidly and reached 29 x 25 x 15 cm in maximum dimension. Radiologic examination demonstrated extensive destruction of the cortical bone of the proximal humerus with infiltration to the surrounding soft tissue. Osteosarcoma, Ewing's sarcoma, and primary lymphoma of the bone were among the differential diagnoses. A trucut biopsy was performed, and microscopic examination revealed a relatively hypocellular lesion composed of fascicles of bland spindled cells with abundant background collagen and rare mitotic figures. The initial diagnosis was desmoplastic fibroma. The family refused surgery, and a short course of chemotherapy was administered. However, due to the aggressive nature of the tumor, a left forequarter amputation was ultimately performed, and additional sections of the lesion revealed numerous islands of cartilage with an exuberant spindle cell component characteristic of FCM. No distant metastases or local recurrence were identified at one year post amputation.

Conclusion: FCM is a benign bone tumor which may present diagnostic challenges due to its aggressive nature. This entity should be considered in the differential diagnosis of bone lesions in children and young adults.

Abstract 24-

Pediatric Renal Tumors Focusing on Unusual Presentations: A Single Institution's 35 Year Experience with Review of 340 Cases

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Background: A broad spectrum of benign and malignant renal tumors occurs in the pediatric population, which represent 8% of all tumor diagnoses in this age group. A thorough understanding of these tumors is crucial to the optimal diagnosis and management of children with renal masses.

Design: A retrospective review of the medical records of children with renal tumors managed between 1975 and 2010 at Children's Healthcare of Atlanta was undertaken to evaluate the incidence and outcome of renal tumors in preparation for comparative genomic hybridization studies.

Results: A total of 340 cases of renal tumors were identified. Wilms tumor was the most common diagnosis (278; 81.8%) and included 259 (93.4%) with favorable histology, 19 (6.6%) with unfavorable histology, 1 (<1%) botryoid case who presented with massive hematuria, 6 (2%) bilateral cases, and 5 (1.8%) congenital cases. Additionally, 5 cases had WT1 abnormalities, and 2 cases had partial monosomy 11. Since enrollment of our Wilms tumor patients in the current COG study # AREN03B2, no loss of heterozygosity (1p, 16q) was identified in 53 patients. Additionally, 1 case of diffuse nephroblastomatosis was identified. Less common were renal cell carcinoma (14, 4.1%; 2 papillary, 2 chromophobe, 1 clear cell, 1 multicystic, 1 unclassified; 4 TF3 positive, 1 TF3 negative, 9 TFE unknown), mesoblastic nephroma (12, 3.5%; 8 cellular, 2 classic, 4 combined), clear cell sarcoma (9, 2.6%), and rhabdoid tumor (4, 1.2%). Nineteen cases (5%) of unusual renal tumors were identified, including primary neuroblastoma (6, 1.8%); primitive neuroectodermal tumor (3, 1.25%); renal medullary carcinoma in sickle cell patients (2, <1%); Burkitt's lymphoma (1, <1%); dermoid cyst of the kidney (1, <1%); angiomyolipoma in tuberous sclerosis patients (3, 1.25%), including 1 conventional and 2 epithelioid variants one of which showed lymph node metastasis; rhabdomyosarcoma (1, <1%); papillary transitional cell carcinoma (1, <1%); and sarcoma not otherwise specified (1, <1%). Follow up of those patients showed survival rates and outcomes comparable to national data.

Conclusion: Our review highlights the great diversity of pediatric renal tumors. We hope that molecular-genetic analyses in phase II of this study will provide a better understanding of the molecular-genetic basis of these lesions and, ultimately, more effective therapies.

Abstract 25-

Amnion Stem Cells in Perinatal Disease

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Background: A proportion of amnion cells in normal term placentas express stem cell markers.* In pathologic conditions, do any amnion cells still express these markers?

Design: Placentas, chorio-amnion membranes and umbilical cords were retrieved from our autopsy files. The fetuses and neonates had a variety of pathologic conditions, listed in the table. H&E stained sections from formalin fixed, paraffin-embedded tissue were examined for the presence of aligned amnion cells. Ten suitable cases were given random codes and prepared for immunohistochemistry (IHC) with antibodies to Oct 4, a nuclear stem cell marker. Oct4(+) amnion stem cells were counted and expressed as a percent of all amnion cells. RT-PCR analyses for both Oct 4 and Nanog were prepared from five deparaffinized specimens, with appropriate controls.

Gestational age / Birth	Pathology	IHC Oct4 (+) cells	RT-PCR (+) Oct4/Nanog
1) 23w / LB	cRPH, LP, SM, CA	19.6 %	+w / +
2) 27w / LB	SP with infarcts	44.4 %	ND
3) 28w / SB	FV, FH	33.6 %	+ / +
4) 29w / SB	SP, VUE, FV, DV, CA	0	ND
5) 29w / LB	FH, LP, M	17.9 %	+ / +
6) 32w / SB	FV, M, subCA	40.6 %	ND
7) 33w / SB	SP, FV, VUE, SM	23.8 %	+w / +
8) 34w / SB	SP	15.3 %	+w / +
9) 37w / SB	FV, DV, SM, CD, CA	0	ND
10) 41w / SB	SP, VUE, M, FMH	32.1 %	ND

Results: With IHC, Oct 4 positive amnion cells are found in 8/10 placentas and are more numerous in preterm placentas without chorioamnionitis. Three cases (1, 4, 9) with chorioamnionitis had significantly lower numbers of Oct 4-positive cells ($p < 0.017$). All 5 tested cases expressed Oct4 and Nanog markers by RT-PCR.

LB - liveborn; SB - stillborn; SP-small placenta (<10%ile); LP-large placenta (>90%ile); VUE-villitis of unknown etiology; FV-fetal vasculopathy; DV-decidual vasculopathy; CA-chorioamnionitis (\geq stage 2); subCA-subchorionitis; cRPH-chronic retroplacental hemorrhage; SM-amnion squamous metaplasia; FH-fetal hydrops; M-meconium; CD-chronic deciduitis; FMH-significant fetomaternal hemorrhage; ND-not done; +w-weak RT-PCR signal

Conclusions: Amnion cells continue to express stem cell markers in a number of pathologic states. Acute chorioamnionitis is associated with a significantly decreased number of amnion cells expressing stem cell markers, possibly because microbial products or inflammatory cytokines produce necrosis/apoptosis of stem cells, or else induce them to mature/differentiate. The functional significance of amnion cells maintaining a stem cell phenotype and the importance of the loss of this phenotype with infection remain to be determined.

*Parolini O, et al. Stem Cells 2008;26:300-311.

*Izumi M, et al. J Reprod Immunol 2009;81:39-43.

Abstract 26-

Autopsy findings in a new case of Acrocephalopolydactylous Dysplasia (Elejalde syndrome)

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Background: Acrocephalopolydactylous Dysplasia (Elejalde syndrome) is a rare, lethal, autosomal recessive disorder marked by organomegaly, craniosynostosis, polydactyly, skeletal dysplasia, and a thick, redundant skin. The underlying pathophysiology is believed to be fibroblast overgrowth resulting in excessive connective tissue in multiple tissues of the body.

Design: A male infant was born by spontaneous vaginal delivery at 34 weeks' gestation to a 16 year old Hispanic primigravida. Prenatal ultrasound had identified fetal abnormalities including a small chest with short ribs, short limbs, abnormal kidneys and oligohydramnios. A tentative antenatal diagnosis of short-rib skeletal dysplasia was made, with a differential diagnosis of Jeune's asphyxiating thoracic dysplasia versus another short-rib polydactyly dysplasia. The infant died within the first hour of life after a brief and unsuccessful resuscitation effort. A standard unrestricted autopsy was performed.

Results: In addition to the sonographically observed abnormalities, autopsy examination revealed numerous additional anomalies that were recognized as characteristic of acrocephalopolydactylous dysplasia (Elejalde syndrome). These included a large globular body with acrocephaly, thick and redundant skin folds in the head and neck region, hemangiomas involving the face and scalp, a small thorax with short ribs, severe shortness of all limb segments, brachypolysyndactyly with six to seven digits in hands and feet, and bilateral popliteal pterygia. There was organomegaly of the liver, brain and placenta. The lungs were markedly hypoplastic; the kidneys were small and cystic; the pancreas was markedly enlarged, cystic and fibrotic; the bowel was malrotated and the spleen was enlarged with multiple accessory spleens. The common microscopic finding in several organs was marked fibrosis with an excess of connective tissue. Tissue cultures were obtained and a normal 46 XY karyotype was obtained. Fibroblasts were noted in the cytogenetics laboratory to grow unusually rapidly in culture, consistent with the only prior cell kinetic study reported in 1977 by Elejalde in the index case. These cultures have been saved for future studies.

Conclusion: This is the seventh known case of Elejalde syndrome. While this infant exhibits numerous characteristic features, our case differs from previously reported cases in some respects, helping to further define this rare disorder. Our fibroblast cultures will hopefully allow further characterization of the biochemical and growth properties of these cells and to test the hypothesis that this entity results from inactivating mutations in a gene for Fibroblast Growth Factor Receptor.

Abstract 27-

Childhood Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): Case Report and Review of Literature

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Background: Childhood blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive neoplasm often encountered in the elderly. It usually presents as a cutaneous lesion in about 85% of cases and is associated with a very poor prognosis. BPDCN is rare in childhood. A recent review reported twenty-one children - nineteen years and younger eleven of whom had skin involvement at presentation. Previously thought to originate from Natural Killer (NK) cells, recent evidence supports derivation from plasmacytoid dendritic cells (PDC).

Design: We report a 12 year old male who presented with an 8 cm indurated, non-tender mass on the lateral aspect of the left lower leg of 3 months duration. Initial therapy consisted of complete excision only but four months later he developed a lump in the left thigh, bilateral inguinal and lower abdominal lymphadenopathy. Lymph node biopsy confirmed this to be recurrent BPDCN. He was commenced on chemotherapy as per T-cell induction (Vincristine, prednisone, doxorubicin and L-Asparaginase) followed by consolidation with 5gm/m² high dose methotrexate. He successfully went into remission and went on to an unrelated, 10/10 HLA-match Peripheral Blood Stem Cell transplantation (PBSCT). The conditioning regimen was VP16, campath, and TBI The patient is disease free 14 months after PBSCT and does not have chronic graft vs host disease.

Results: Histology of the initial excised mass and the subsequent lymph node biopsy revealed a diffuse infiltrate of monomorphous small to medium sized cells with irregular and twisted nuclear contours with dispersed blastic chromatin, occasionally distinct nucleoli and scant cytoplasm, involving the dermis and subcutaneous adipose tissue. The lesional cells expressed CD4, CD56, CD123 and CD45. The lesional cells did not express CD2, CD3, CD5, CD8, CD10, CD20, CD30, CD34, CD57, Cd79a, PAX5, Alk1 and Granzyme-B. In situ hybridization for Epstein-Barr virus was negative. The morphology and immunophenotype were diagnostic of BPDCN.

Conclusion: Non dermatological presentation of BPDCN among children is rare. The prognosis among childhood cases is variable which may be related to the lack of a standardized treatment approach to this disease. No single prognostic indicator has been isolated other than response to treatment. Due to its rarity, no conclusions can be drawn about long-term survival. Our patient is doing well at last follow up.

Abstract 28-

Pediatric T Cell Rich Large B Cell Lymphoma: an Under-recognized Entity?

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Background: T-cell-rich large B-cell lymphoma (TCRLBCL) is a distinct subtype of diffuse large B cell lymphoma which is under-recognized in the pediatric population. A meticulous workup is necessary to avoid misdiagnosing it as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) or classical Hodgkin lymphoma (HL). Few children with advanced stage were described to date. We report 2 pediatric patients with high stage TCRLBCL and highlight their pathological features.

Design: Two cases of TCRLBCL were diagnosed at The Children's Hospital of Wisconsin between the years 1997 and 2010. Pathology and clinical course were reviewed.

Results: We report two pediatric patients who had diffuse lymphadenopathy and multiple liver lesions at presentation. Clinically both patients were suspected to have Hodgkin lymphoma. The first patient, a 15 year old boy presented with a 2 month history of progressive back pain and weakness in the lower extremities. He had axillary and retroperitoneal lymphadenopathy, multiple liver lesions as well as an extradural mass producing cord compression. Pathology from the extradural mass showed a proliferation of atypical cells with large lobulated nuclei and dispersed chromatin that were CD45+, CD20+, CD3-, CD30- and CD15-. The background cellular infiltrate was composed entirely of CD3 positive T lymphocytes. CD21 failed to show a residual dendritic cell meshwork and CD57 showed only a rare positive cell. The bone marrow showed extensive involvement by a malignant process consisting of few large atypical cells in a background of many benign T lymphocytes. Electron microscopy performed on the extradural mass was interpreted as positive for "popcorn cells".

The second patient, a 17 year old girl with a five month history of fatigue, weight loss and night sweats was found to have mediastinal, hepatic, splenic and mesenteric lymphadenopathy as well as multiple liver lesions. Liver biopsy and excisional biopsy of a mediastinal lymph node confirmed TCRLBCL.

Both patients had an excellent response to chemotherapy and one remains in complete remission 10 years after the initial diagnosis.

Conclusion: TCRLBCL remains a diagnostic pitfall for the pediatric pathologist. A strong degree of suspicion with emphasis on immunohistochemical staining is required to reach the diagnosis. While establishing molecular clonality may be helpful, this is usually limited by the small number of malignant cells. As evidenced by our patients, children respond well to chemotherapy and have a very good prognosis. To our knowledge, only one pediatric case of TCRLBCL with bone marrow involvement has been previously reported.

Abstract 29-

A Simple Method for Evaluation of Villous Morphology in Conjunction with Routine Histological Examination

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Background: The purpose of this study was to find a practical method to evaluate the complex placental villus architecture abnormalities, when routine hematoxylin and eosin stained sections were insufficient.

Developmental abnormalities in the placenta have gained more significance in recent years after the molecular and morphological mechanisms of villous growth have been elucidated. Steps of initial branching and later non-branching angiogenesis result in variable and different morphology. Most of the techniques used to demonstrate the 3-D morphology of chorionic villi are scanning electron microscopy and at times, confocal fluorescent microscopy. These techniques are difficult, labor-intensive and expensive. In addition most hospital centers do not have the scanning electron microscopy facilities.

Design: During the study period of 18 months, 398 products of conceptions and 55 placental samples were examined using a dissecting microscope made by Olympus and digital images were obtained using the same device. The products of conception specimens were examined after placing them in a petri dish filled with normal saline. This yielded very useful and esthetically pleasing images. The placental samples were more difficult to manipulate. Teasing the chorionic villi usually destroyed the structures. After thinly slicing an unfixed placenta slice, we left specimen in normal saline overnight in a refrigerator. Next morning the teasing process was much more effective and the results were more satisfying. The gestational ages of the products of conception specimens ranged from 6 to 19 weeks gestational age. The placental cases this range was 26 weeks to term gestation.

Results: In this pilot study we were able to examine 398 products of conception samples using a simple Petri dish, normal saline and a dissecting microscope. Similar techniques were applied to 50 placentas normal or with growth disorders. The branching and non-branching angiogenesis and their effects on the morphology of the chorionic villi were clearly seen. The placental samples were more difficult to handle and they did not yield as good images as expected. But the process itself was deemed useful when the correlation with the regular hematoxylin and eosin stained slides.

Conclusions: The rapidly collecting new information about the methods of villous growth and its dependence on the vasculogenesis and angiogenesis prompted us to find simple morphological methods for teaching purposes other than utilizing the routine hematoxylin and eosin stained sections to correlate the morphology. We think that with some modifications, this has the potential to be a very useful educational tool.

Abstract 30-

Pediatric Acute Myeloid Leukemia With t(8;16)(p11.2;p13.3) Shows Unique Clinical, Morphological, and Immunophenotypic Features: Report Of Three Cases

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Background: Acute myeloid leukemia (AML) with t(8;16)(p11.2;p13.3) is a rare subtype of AML described mostly in adults with a significant proportion of therapy-related cases. It presents as a leukemia with monocytic and/or monoblastic differentiation with frequent hemophagocytosis and disseminated intravascular coagulation (DIC). Recent literature shows that this subtype has unique morphological, immunophenotypic, cytogenetic, molecular, and prognostic features but is not yet a distinct diagnostic entity in the 2008 World Health Organization Classification. Infants and children are also underrepresented in recent studies. We describe three pediatric cases with both novel and classical findings.

Design: Retrospective case series from two tertiary Children's Hospitals over a 10-year period. The clinical course, pathology, and cytogenetics were reviewed.

Results: 3 patients (ages 1 month, 5 years, and 8 years) were identified with AML with t(8;16)(p11.2;p13.3). Two were de novo cases and one followed a bone marrow transplant for therapy-related myelodysplastic syndrome, which harbored the same isolated translocation. The infantile case presented with an extreme leukocytosis (381,000/ul), DIC, and leukemic involvement of both cerebrospinal fluid and skin. Only one case showed blast hemophagocytosis and prominent cytoplasmic vacuoles. Cytomorphology was characterized by parallel positive myeloperoxidase (MPO) and non-specific esterase staining in the two de novo cases. Cases showed monocytic or monoblastic differentiation (FAB M4, M5a, M5b), and demonstrated characteristic immunophenotypic features, including CD34-/CD56+ blasts, by flow cytometry on peripheral blood or bone marrow aspirates. Each patient underwent hematopoietic stem cell transplantation. The two patients with de novo presentations are alive at 3 months and 19 months following transplant; the patient with therapy-related AML died less than one year following diagnosis.

Conclusions: Pediatric acute myeloid leukemia with t(8;16)(p11.2;p13.3) has similar features to cases described in adults. It is typically clinically aggressive, especially in therapy-related cases. Morphologic and immunophenotypic findings may be diagnostically helpful; however, MPO positivity and CD34 negativity may present pitfalls. More data are needed to determine if features of this subtype apply to younger age groups. Further investigation of the 8p11 fusion gene (MYST3), since it is found in both de novo and therapy-related cases, may provide crucial leukemogenic clues and potential therapeutic targets.

Abstract 31-

Intracellular Presence Of Helicobacter pylori In The Gastric Epithelium And Lamina Propria In Children

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Background: Helicobacter pylori (Hp) is generally accepted to be non-invasive though there are recent reports of its identification in the epithelium and lamina propria (LP). Our objective was to determine the presence of Hp within gastric epithelium and LP, henceforth referred to as extraluminal Hp (eHp).

Design: Gastric biopsies from pediatric patients undergoing upper endoscopy between Jan 2006-Dec 2007 were evaluated. Inclusion criteria were Hp infection based on histology and age less than 18 years. Only the first biopsy for each patient was included. Exclusion criteria included Crohn's disease. Pathology evaluation of gastric biopsies included application of the revised Sydney analog scale. The anti-Hp immunoperoxidase stain was used to assess mucosal distribution and eHp. Acid suppression use was elicited via review of medical records.

Results: 46 cases met study criteria. Mean age of patients was 11 years (range 1-17) and 46% female. Both antral and oxyntic biopsies were present in 43.5% of cases, antral only in 50% and oxyntic only in 6.5%. Chronic inflammation was mild in 13%, moderate in 43.5% and marked in 43.5%. Activity was not seen in 11%, mild in 37%, moderate in 48%, and marked in 4%. There was foveolar hyperplasia in 26%, lymphoid follicular hyperplasia in 50%, and eosinophilia in 24%. Of all the biopsies, Hp was seen in the LP in 61% and intracellularly in 70%.

Prior to endoscopy, 57% were on acid suppression. Those on acid suppression were less likely to have marked antral surface density (20% vs. 56%) and marked foveolar density (48 vs. 83%). Though there were few oxyntic biopsies, this trend also held true. There did not appear to be a correlation between the use of acid suppression and eHp.

There did appear to be a correlation between the organism density and eHp, for example with marked Hp density on the antral surface, eHp was seen in 73% compared to 62% for moderate density, and 57% for mild density. Additionally, for marked foveolar density, 67% had eHp compared to 55% for moderate density and 60% for mild. eHp was more frequent in oxyntic biopsies, where the organisms were often seen in parietal cells. All oxyntic biopsies with marked surface density had eHp compared to 75% with moderate density. For the oxyntic neck, all of the marked density biopsies had eHp compared to 60% for the moderate density.

Conclusion: This study supports previous observations of Hp within the gastric epithelium and the lamina propria. In our small study, organism density seems to be directly linked to the potentially invasive behavior. Acid suppression appears to decrease the density of organisms but not the extraluminal migration.

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Abstract 32-

An Attempt To Apply A Recent NICHHD Workshop Consensus Stillbirth Classification Into Practical Use

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Background: Unlike cause of death determination in liveborn individuals, it is the exception rather than the rule that a fetal death is ascribable a single underlying condition. Therefore, recent attempts have been made to classify stillbirths in a more practical and realistic manner by identifying those relevant conditions present at the time of fetal death that made some contribution to the stillbirth. As proposed in the executive summary of the 2007 National Institute of Child Health and Human Development (NICHHD) Workshop , an ideal classification system would be a single, standardized, international scheme that would identify potential causes of stillbirth and provide a likelihood or probability with which the death could be attributed to these factors. The purpose of this study was to determine to what degree this consensus classification could be applied practically to actual cases in an academic perinatal pathology practice.

Design: The author conducted a retrospective review of fetal autopsies performed on stillbirths between August 2004 and April 2010 at a single academic institution. For each of the cases, relevant fetal, placental, maternal, and external risk factors were identified. Given these multiple factors, an attempt was made to identify a single underlying condition that played the most significant role in causing the fetal death (i.e., in initiating the sequence of events leading to fetal demise).

Results: A total of 39 cases was identified; gestational ages ranged from 16 to 39 weeks. Six were excluded since they were elective terminations. Of the 33 remaining cases, 17 (51%) could be attributed to a discrete underlying entity (cause); 5 (15) remained entirely undetermined; 3 (9%) had an identifiable mechanism (i.e., perinatal asphyxia) without a discernible underlying etiology; and the remaining 8 (24%) offered associations rather than underlying causes.

Conclusion: In approximately half of the cases (49%), a single condition was insufficient to independently trigger the fetal death sequence; the explanation of the death required the inclusion of multiple conditions that would be described most accurately as associations or factors rather than causes.