Pediatrics

1562 Omental Fibromyxoid Tumor (OFT): A Distinctive Variant of Inflammatory Myofibroblastic Tumor? A Clinicopathologic and Immunophenotypic Analysis

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Background: OFT, described by Gonzalez-Crussi as omental-mesenteric myxoid hamartoma, is considered part of the morphologic spectrum of IMT. It occurs in infants as abdominal nodules composed of mesenchymal and inflammatory cells in a myxoid stroma. We retrospectively investigated a series of OFT and compared their clinicopathologic and immunohistochemical features to classic IMT in order to explore their biological relationship.

Design: H&E stained section from 5 OFT and 11 abdominal IMT were evaluated as well as smooth muscle actin, desmin, ALK1, cytokeratins (AE1/AE3, Cam 5.2) and WT1 expression. Clinicopathologic information was retrieved from medical records.

Results: The mean age was 0.8 years for OFT and 8 for IMT. Mean follow up, available in all cases, but one OFT, was 4.6 years. All patients are disease free, after relapses in 1 OFT and 3 IMT. Histologically, OFT showed a myxoid stroma with hyalinized vessels, stellate or elongated mesenchymal cells and a discrete lymphocytic infiltrate, often perivascular . Pleomorphism and necrosis were absent, mitoses rare. IMT had a variable morphology, with myofibroblasts, ganglion-like cells and a prominent inflammatory infiltrate. A myxoid background was present in 3 cases and necrosis in 2. Mitoses were 2 to 7/HPF. Immunohistochemically, 90% of OFT and IMT expressed SMA. Desmin and cytokeratins were diffusely positive in OFT and only focally positive in 4 and 3 IMT respectively. Nuclear staining for WT1 was seen in OFT, but absent in IMT (although a cytoplasmic positivity was noted in 4). 4 OFT showed a peculiar dot-like ALK staining, whilst 4 IMT displayed a cytoplasmic positivity. Cytogenetic analysis in one OFT revealed a chromosomal mosaicism with inversion of chr 2(p14-16q37).

Conclusions: OFT may represent an infantile variant of IMT, with characteristic clinicopathologic, immunophenotypic and genetic features. OFT are histologically more homogeneous than IMT, with a prominent myxoid background and a bland cytology. The expression of cytokeratins and desmin and the nuclear staining for WT1, suggest a possible origin from sub-mesothelial fibroblasts. The dot-like pattern of ALK staining might not be related to a rearrangement of ALK gene, an hypothesis supported by the inversion of chr 2 in a different locus in one case. Further studies will clarify the cytogenetic features and the prognosis of OFT.

1563 Melanotic XP11 Translocation Renal Cancer: A Distinctive Neoplasm with Overlapping Features of Pecoma, Carcinoma, and Melanoma

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Background: Gene fusions involving the transcription factor gene *TFE3* have been implicated in 2 types of cancer, alveolar soft part sarcoma (ASPS) and the Xp11 translocation renal cell carcinoma (RCC). Recent reports of strong nuclear labeling for TFE3 protein by immunohistochemistry (IHC) in perivascular epithelioid cell neoplasms (PEComas), comparable in intensity to that seen in neoplasms with documented *TFE3* fusions, have suggested the possibility of *TFE3* gene fusions in some PEComas.

Design: We describe two cases of malignant melanotic epithelioid renal cancers bearing *TFE3* gene fusions. Their phenotype overlaps with PEComa, Xp11 translocation RCC, and melanoma, but most closely resembles PEComa.

Results: Both neoplasms occurred in children (ages 11 and 12), and presented with distant metastases. Both featured sheets of epithelioid cells with clear to finely granular eosinophilic cytoplasm set in a branching capillary vasculature. The neoplastic cells contained variable amounts of fine brown pigment confirmed to be melanin by Fontana Masson histochemical stain. By IHC, the neoplastic cells labeled for melanocytic markers HMB45 and Melan A, but not for S100 protein, MiTF, or any epithelial, renal tubular, or muscle markers. Both neoplasms demonstrated nuclear labeling for TFE3 protein by IHC, and the presence of *TFE3* rearrangements was confirmed by fluorescence in situ hybridization (FISH) analysis using a *TFE3* break-apart probe. In case 1 (male), the rearrangement was unbalanced, while in case 2 (female), the rearrangement was balanced with loss of the second X chromosome.

Conclusions: These distinctive neoplasms combine morphologic features of PEComa, Xp11 translocation RCC, and melanoma, although the phenotype most closely resembles PEComa. The present 2 cases represent the first documented examples in which *TFE3* rearrangements co-exist with melanin production, and their identification raises the possibility that *TFE3* gene fusions may underlie an aggressive subset of lesions currently classified as PEComa in young patients.

1564 Malignant Rhabdoid Tumors: A 12 Year Experience

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Background: Malignant rhabdoid tumors (MRT) are rare childhood neoplasms. Although originally described in the kidney, these tumors have now been identified in various locations including the liver, soft tissue, and the central nervous system. The purpose of this study was to review the clinicopathologic features of rhabdoid tumors identified over a 12 year period at a tertiary pediatric medical center, and also to stress the proper classification of these tumors as currently more aggressive therapy has led to improved survival.

Design: A retrospective review from January 1st,1996 to September 10th, 2008 identified 20 patients who were diagnosed with MRT. These patients were analyzed: age at diagnosis, site of tumor, histology, immunohistochemical profile, and mortality.

Results: MRT were identified in 10 males and 10 females. The median age at diagnosis was 27.5 months. The lesions were located in a wide variety of anatomic sites including CNS (9), liver (2), kidney (2), mediastinum (1) and soft tissue (6). Histologically, most tumors were "Malignant small blue cell tumors", and the majority showed at least focal "rhabdoid" morphology. Immunohistochemical stains showed characteristic poly phenotypic pattern: positive for vimentin, cytokeratin/epithelial membrane antigen (EMA) and smooth muscle actin (SMA) in all cases. Some MRTs showed scattered positivity for GFAP, CD31, CD34, CD117, CD99 and Myogenin. BAF-47 staining showed loss of normal nuclear positivity in tumor cells of all cases. Clinically, prior to 2006, most patients (7 of 9) died of disease, and one had metastasis despite treatment. Since 2006 one patient was lost to follow up, and only 2 patients have died (one soft tissue, one kidney). The remaining patients have undergone treatment with a more aggressive chemotherapy with or without radiation, and as of date have no evidence of recurrence or metastasis.

Conclusions: In our experience, MRT present with varied morphology and do not always show classic "rhabdoid" features. The tumors show polyphenotypic immunostaining pattern and loss of normal nuclear positivity for BAF-47. With recent changes in therapeutic approach, over 50% of our patients have longer survival. Because of the varied morphology and immunophenotypic expression, use of restricted immunostains could result in a misdiagnosis. It is therefore important to consider this tumor in the differential diagnosis for all "Malignant small blue cell tumor", emphasizing the need to perform BAF47 immunostaining in all cases.

1565 Activation of Canonical Wnt Signalling Inhibits Proliferation or Promotes Differentiaiton in High-Grade Osteosarcoma

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Background: Osteosarcoma (OS) is the most frequent primary malignant bone tumor. High-grade central OS frequently affects children and young adolescence. The prognosis has changed dramatically after the introduction of neoadjuvant chemotherapy, but the overall survival has reached a plateau. Frequent locations of OS at metaphysis of long bones as well as the age of the patients during the most rapid bone growth suggest that the pathogenesis of OS is closely related to high bone turnover. Recent research has demonstrated that canonical wnt pathway is required for osteogenic linage differentiation. Active wnt signalling contributes to carcinogenesis, however, little is known about the possible involvement of bone differentiation pathway in OS.

Design: A canonical wnt signalling luciferase reporter construct was transfected in 4 OS cell lines. β-catenin expression was determined in 4 OS cell lines and a tissue array consist of 144 OS samples from 88 patients .The effect of wnt signalling modulation on cell proliferation as well as osteogenic differentiation capability was assessed.

Results: Canonical wnt signalling is not active in 4 OS cell lines as determined by the luciferase reporter assay. Negative nuclear β-catenin staining was found in all 4 OS cell lines and 87% of cases in our OS tissue array. Upregulation of wnt signalling was determined upon treatment with GIN(GSK3β inhibitor) by reporter assay as well as β-catenin translocation to the nuclear in 4 OS cell lines by immunofluorescence staining. Around 50% inhibition of cell growth was observed in MG-63 and U-2-OS with high level of GIN-mediated activation of wnt signalling. However, little inhibition was found in SJSA and HOS cell lines, which had low level of wnt restoration. SJSA and HOS but not MG-63 and U-2-OS cell lines retain capablity toward osteogenic differentiation. Stimulation of wnt signalling enhances ALP (alkaline phosphatase) activity and mineralization in SJSA and HOS but not MG-63 and U-2-OS.

Conclusions: Wnt signalling is shown to be inactive in osteosarcoma. Activation of wnt sigalling has been known for involvement in carcinomagenesis, however, here we show that restoration of wnt sigalling inhibits cell proliferation or promotes osteogenic linage differentiation in osteosarcoma cell lines.

1566 Lipoblastoma (LPB): A Clinicopathologic and Immunohistochemical Analysis of 59 Patients

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Background: LPB is a benign neoplasm that occurs predominantly in early childhood. We investigated clinicopathologic features, associated conditions, immunohistochemistry, and outcome.

Design: 59 LPB were identified from surgical pathology and consultation files. Pathology materials, cytogenetics reports, and medical records were reviewed. Immunohistochemistry for S100 protein, CD34, MDM-2, and Mib-1 was performed on formalin-fixed, paraffin-embedded tissue using standard techniques.

Results: 59 patients had 74 samples including 13 with local recurrence. There were 37 males and 22 females (ratio 1.7). Age at diagnosis ranged from 3 months to 16 years with 22% in the first year, 68% at 1-9 years, and 10% at 10-16 years. 64% arose on the trunk, 27% on the extremities, and 8% in the head/neck. 46% had recurrence. Tumor diameter ranged from 1.2 to 15.5 cm. The white to yellow cut surface showed variable lobulation and myxoid change. Histologically, nodules of adipose and myxoid tissue were demarcated by bands of fibrous tissue. The cells displayed a range of differentiation from multivacuolated lipoblasts to mature adipocytes. Mitoses were nonexistent to rare. Histologic variations included subtle zonal architecture of fatty maturation, abundant myxoid material, primitive mesenchymal cells, a focal plexiform vascular pattern, multinucleated cells, a mast cell infiltrate, and extramedullary hematopiesis. All cases were immunoreactive for S100, CD34, and MDM-2. Mib-1 reactivity was 0.5%. Cytogenetic analysis demonstrated a variety of chromosome 8 abnormalities in 8 cases. 10 patients had a variety of clinical abnormalities including macrocephaly,

seizures, developmental delay, autism, congenital anomalies, Sturge-Weber syndrome, or a family history of multiple lipomas.
Conclusions: This large series of LPB confirms its occurence in older children and adolescents, documents a recurrence rate of 46% and confirms that the degree of adipocytic differentiation does not predict biologic behavior. An unexpected finding was the presence in 17% of patients of central nervous system disorders including seizures, autism, and development delay, congenital anomalies, Sturge-Weber syndrome, or a family history of lipomas. These observations raise the question of whether predisposing genetic or other constitutional factors contribute to the development of LPB.

1567 Spontaneous Intestinal Perforation and Neonatal Necrotizing Enterocolitis: Two Distinct Clinicopathological Entities

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Background: Intestinal obstruction and perforation are serious problems in the premature neonate. They can be due to mechanical factors or necrotizing enterocolitis (NEC). Often, no apparent cause can be identified clinically. This is referred to as spontaneous intestinal perforation (SIP). The histological changes in SIP are at present poorly characterized and its pathogenesis is unknown. To this end, we performed a detailed comparison of the clinical and histological features of SIP and NEC.
Design: Clinical files and biopsy material from all neonates treated surgically for NEC (n = 25) or SIP (n = 40) in the period 1991–2008 were reviewed. Biopsies were also stained for alpha-smooth muscle actin, S100 protein, c-kit protein and Cathepsin D.
Results: SIP patients had more often been exposed to antenatal corticosteroids. They had a lower birth weight and were more commonly treated with dexamethasone in the early neonatal period. Occult or frank blood in the stools and systemic symptoms were more common in NEC. The histological evaluation showed a segmental absence of the intestinal musculature (SAM) in dilated bowel segments or close to a perforation in all SIP cases, and in none of the NEC samples. SAM typically affected the circular muscle layer. Gaps in this structure were filled with connective tissue similar to that found in the normal submucosa. The architecture and composition of the myenteric plexus were always preserved.
Conclusions: In our series, segmental absence of the intestinal musculature was specific for SIP and moreover present in all such cases. A compilation of previous publications showed a much lower frequency (14%). The reason for this discrepancy may be that SAM can be very localized and requires diligent searching. On the basis of the histological characteristics of SAM, we believe that it occurs before birth. A short period of localized ischemia in a zone of SAM might be sufficient to cause "spontaneous" bowel perforation in the neonate.

1568 Survivin, Bcl-2 and Caspase 8 Expression in Wilms Tumors with Favorable Histology Does Not Correlate with Clinical Stage

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Background: Patients with favorable histology Wilms tumors (FHWT) have a survival rate of approximately 90%. The only way to further improve the survival of these patients is to identify novel molecular prognostic markers that could lead to their stratification, allowing selective augmentation of therapy for high risk patients and avoiding adverse therapeutic effects in the remaining patients. Anti-apoptotic proteins, such as survivin and bcl-2, inhibit tumor cell response to chemotherapeutic agents and pro-apoptotic proteins, such as caspase 8, are necessary for induction of apoptosis by novel experimental therapeutic agents, such as TRAIL. Therefore, we decided to study experssion of these proteins in FHWT and to correlate their expression with clinical stage.
Design: Tissue arrays containing a total of 59 pediatric FHWT samples from the files of the National Wilms Tumor Study Group (NWTSG) were studied by immunohistochemistry for the expression of survivin, bcl-2 and caspase 8. The age of the patients ranged from 6 to 120 months (mean 58 months). Twenty-six were males and thirty-three females. Twelve patients were stage I, eighteen stage II, twenty stage III, six stage IV, and three stage V. Twenty one cases were blastemal predominant tumors. Paraffin embedded tissues were stained using regular immunostain protocols. An immunohistochemistry score was generated by mulplying the intensity of the staining (0, 1+ and 2+) with the percentage of positive cells (0, 1=1%-25%, 2=26% to 49%, 3=50% to 75% and 4=76% to 100%). Low expression was defined as Score 1-4 and high expression as score 6-8.
Results: FHWT expressed high levels of survivin in 44% of the cases, and high levels of bcl-2 in 46% of the cases. Caspase 8 expression was absent or low in 81% of the cases. No overt correlation between protein expression and clinical stage was observed. Blastemal-predominant tumors did not show significantly different expression of these proteins when compared to intermediate tumors.
Conclusions: The data show that high expression of survivin and bcl-2 in Wilms tumors is common and may define high risk disease in all stages. No or low caspase 8 expression suggests that TRAIL may not be a successful therapeutic alternative, unless proper steps to increase caspase 8 expression are taken prior to its administration.

1569 Expression of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) Receptor DR5 in Ewing Sarcoma Family Tumors (ESFT)

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Background: TRAIL induces apoptosis in a wide range of tumor cells but not in normal tissues and is a promising candidate for novel anticancer therapies. The efficacy of a TRAIL agonistic antibody in pediatric sarcomas is currently studied in phase I clinical trials. TRAIL induces apoptosis through binding with two cell surface death receptors (DR), DR4 and DR5. Each one of the TRAIL death receptors is independently sufficient to induce apoptosis, but DR5 is more frequently expressed in tumors and can be induced by chemotherapeutic agents. We have previously shown that ESFT, which are common bone and soft tissue sarcomas in children and young adults, express TRAIL receptors *in vitro* and *in vivo*. However, immunohistochemical studies in paraffin tissues do not provide information of receptor expression on the tumor cell surface, which is necessary for the functionality of the receptors. Also, studies on established cell lines may not be indicative of the expression status of the receptors *in vivo*. To address these questions, we studied DR5 expression in early passage primary cell cultures and corresponding tumor tissues from ESFT patients. We also studied DR5 inducibility by doxorubicin.
Design: Eight early passage ESFT cell cultures were established in our laboratory (TC-324, TC-389, TC-390, TC-392, TC-393, TC-394, TC-399 and TC-400) and studied for expression of DR5 by Western blot and flow cytometry. Six available tumor specimens corresponding to the primary cultures were studied by immunohistochemistry for DR5 expression. Five of these cultures were treated with low to high concentrations of doxorubicin (0.1, 0.5 and 1.0ug/ml) for 16 and 24 hours and DR5 protein expression was studied by Western blot before and after treatment.
Results: All primary cultures expressed moderate to high levels of DR5 by Western blot. Flow cytometric analysis showed high DR5 surface expression in 5 and low in 3 cases. Immunohistochemical staining correlated with the flow cytometric data, as it was high in the 3 studied tumors with high flow cytometric expression and low or absent in the 3 tumors with low DR5 expression by flow cytometry. DR5 expression was induced in all five studied lines even by low concentration of doxorubicin (0.1ug/ml).
Conclusions: DR5 is expressed on the surface of ESFT cells and is induced by doxorubicin. These data suggest that ESFT are amenable to treatment with TRAIL alone or in combination with chemotherapeutic agents, which can increase TRAIL sensitivity at non toxic concentrations.

1570 Characterization of Placental Pathology in Sickle Cell Disease and Sickle Cell Trait Patients

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Background: The homozygous form of sickle cell disease (SCD) occurs in 1 out of 400 African Americans. Additionally 8% of African Americans have sickle cell trait (SCT), underscoring its prevalence in our society. It is thought that most of the alterations in sickle cell patients' placentas are caused by sickling of erythrocytes, leading to regional hypoxia. Comparing the fetal membranes, the umbilical cord, and the placental disk with normal placentas and correlating their relationship to pregnancy outcome will help our understanding of the importance of changes that occur in these groups of patients.
Design: Archival formalin-fixed paraffin-embedded placental tissues from SCD (n=6), SCT (n=24) and healthy (n=30) in-house patients between 2004 and present were reviewed. In addition, clinical information for each patient and the newborn was obtained to evaluate clinical, hematological, and obstetrical information.
Results: Sickled erythrocytes were seen in 100% of placentas from SCD patients, and in 90% of placentas from SCT patients vs. no sickled erythrocytes seen in normal placentas. ($p<0.0001$, Chi Square).

Table-1: Placental findings

	Weeks gestation	Placental weight (g)	Fetal weight (g)	Cord length (cm)	% with villitis of unknown etiology	% with meconium staining	% with advanced villous maturation
SCD (n=6)	37.9	515.5	3099.0	47.5	25	33	70
SCT (n-24)	37.3	526	3039.1	41.6	24	23	71

Table-2: Maternal and fetal factors

	Age	% with DM	Average APGAR at 1 and 10 min	% C-section	Maternal RBC	Maternal Hgb	Bleeding (mL)
SCD (n=6)	27.8	17	8.5-9	33	3.3	9.1	450
SCT (n=24)	27.5	23	7.4-8.3	46	4.01	11.8	510

Conclusions: When evaluating the placenta in a mother with either SCD or SCT, the pathologist should pay close attention to the presence of sickled cells in the intervillous space, advanced villous maturation, villitis of unknown etiology, and meconium staining of the placenta. Each of these histological and morphological features is associated with increased stress to the fetus, and therefore should be correlated with fetal parameters and general fetal well being. Future studies are needed to understand the long term effects of these findings in newborns. The pathologist may be helpful to raise the possibility of sickle cell trait in a previously undiagnosed female by careful observation of erythrocyte morphology in intervillous space.

1571 Incidental Primary Bronchioloalveolar Carcinoma-Like Lesions in Young Patients with Pediatric Malignancies: Histopathologic and Molecular Features

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Background: Primary lung adenocarcinoma is extremely rare in the pediatric age group. There have been anecdotal reports of lesions that histologically resemble usual bronchioloalveolar carcinoma (BAC) in young patients after treatment for non-pulmonary cancers. Here, we present clinical, histopathologic, and molecular data on a single-institution series of seven such cases.
Design: All cases were identified in the course of clinical care. Specimens were from open thoracotomies or thorascopic biopsies. Molecular studies for *EGFR* and *KRAS* mutations were performed in five patients with sufficient material using DNA extracted from paraffin-embedded tissues.
Results: All seven patients were nonsmokers, three male and four female. Median age at original cancer diagnosis was 14 years (range 3-23). Four had osteosarcoma (OS), one mesenchymal chondrosarcoma (MCS), one Wilms tumor and one neuroblastoma. All had received intensive chemotherapy. Median age at diagnosis of pulmonary BAC-like lesions was 15 years (range 10-24). All lesions were found incidentally either by preoperative CT (n=3) or at time of surgery. Retrospective review showed that in at least three patients the nodules were present prior to chemotherapy. Their sizes ranged from 0.1 to 0.6 cm. The histopathology ranged from AAH, to BAC, to mixed subtype

with acinar or papillary features. In three patients, the BAC-like nodules were multiple and co-existed with lung metastases of the original cancer. Of five tumors tested, one was positive for the *EGFR* L858R mutation (patient with prior OS) and another was positive for *KRAS* G12V (patient with prior MCS); the remaining three were negative for common *EGFR* and *KRAS* mutations. Six patients have remained well with a median follow-up of 8 months (1-29 months).
Conclusions: Incidental BAC-like lesions in patients with pediatric cancers can show typical lung adenocarcinoma-type mutations and may not always be chemotherapy-related. Other possibilities include a selection bias effect due to enhanced radiographic scrutiny, a common predisposing germline alteration, or a common prior mutagenic exposure. The natural history and management of this entity remain to be better defined.

1572 Types of Maternal Hypertensive Disease and Their Association with Pathologic Lesions and Clinical Factors

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Background: Hypertensive disease during pregnancy (HD) includes chronic hypertension (HTN), pregnancy induced hypertension (PIH) and preeclampsia/eclampsia (PEC). Although certain clinical factors and placental lesions have been associated with HD in general, differences between types of HD have not been well studied.
Design: Medical records and Surgical Pathology files were searched for placentas with a clinical history of HD and for gestational age matched controls. 206 cases were obtained in each group. In the HD group, 56 had HTN, 78 had PIH and 72 had PEC. Various lesions and clinical factors were compared between the HD groups and controls and between groups of HD. Student's t-test, ANOVA and Chi-square were used to analyze the data.
Results: HD as a group had a higher incidence of placental lesions classically associated with hypertension: decidual vasculopathy ($p<0.001$), infarcts ($p<0.001$), ischemic changes ($p<0.001$), increased perivillous fibrin ($p=0.001$) and chronic deciduitis ($p=0.002$). The control group had a higher incidence of meconium (MEC)($p=0.001$) and acute chorioamnionitis (ACA)($p=0.005$). HD was also associated with lower Apgar scores ($p=0.010$, 0.026), IUGR ($p<0.001$), and delivery at an earlier gestational age (GA) ($p=0.001$). When the HD groups were compared to each other, only GA and IUGR retained significance ($p=0.001$, 0.019). Interestingly, IUGR was less common in the PIH group (6.4%) compared to the HTN (19.6%) and PEC (16.7%) groups and was not different from the incidence of IUGR in the control group (5.9%). GA at delivery was lowest in the PEC group (34.1 weeks) compared to the HTN (37.3 weeks) and PIH (38.0 weeks) groups, both of which were similar to control (37.8 weeks).
Conclusions: As expected, HD is associated with placental lesions of malperfusion as well as adverse clinical factors. In addition, controls showed less chronic and more "acute" lesions (ACA, MEC), than HD cases. Control cases were likely submitted due to intrapartum conditions such as nonreassuring tracings, which may correspond to the presence of meconium or chorioamnionitis in the placenta. Finally, comparisons of HD groups showed differences only in GA and IUGR, and this was seen only in the HTN and PEC groups and not the PIH group. This suggests that PIH may be associated with less severe clinical disease while showing similar pathologic features.

1573 Hemophagocytic Lymphohistiocytosis (HLH): Review of Bone Marrow Morphology and Correlation with Laboratory Findings

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Background: HLH is a life-threatening disease, primarily affecting children, characterized by uncontrolled proliferation of activated lymphocytes and histiocytes driven by a cytokine storm. Hemophagocytosis is the hallmark of HLH. Histologic examination of bone marrow (BM), one of the most frequently involved organs, is critical for diagnosis. However, BM morphologic findings of HLH are not fully characterized. The aim of this study is to evaluate the BM morphologic features of HLH and correlate them with laboratory findings.
Design: We retrospectively reviewed BM smears and biopsies of 40 patients (pts) with HLH (diagnosed based on 2004 guidelines) and a control group (CG) of 21 cases of HLH clinical and morphologic mimics. We designed a grading system of hemophagocytic activity (HA) based on the frequency of hemophagocytosis in the BM smear and compared morphology between the two groups.

Grading of HA

Grade	# of Hemophagocytic figures
0	Absent
1	Rare (<5/smear)
2	Occasional (>10/smear)
3	Easily seen on 10X
4	Easily seen on 4X

Clinical and laboratory data were collected and correlated with morphologic findings.
Results: HLH pts and CG aged 0.2 to 27 yrs (average=6.9 yrs). Average BM cellularity was 76% in HLH pts compared to 68% in CG (no significant difference). HA was present in 88% of HLH pts. A significant increase in histiocytes and atypical lymphocytes was seen in a significantly higher proportion of HLH pts compared to CG ($p<0.05$). HLH pts showed a significantly higher grade of HA compared to CG ($p<0.05$). The engulfed hematopoietic cells were intact in HLH. In contrast, they were degenerated and accompanied by cellular debris and hemosiderin pigment in HLH mimics. The grade of HA in HLH BMs did not correlate with cytopenias, Ferritin or Triglyceride levels, natural killer or cytotoxic T cell function, Perforin expression, CD4/CD8 ratio, or soluble IL-2 receptor levels.
Conclusions: BM examination is critical for HLH diagnosis and has a sensitivity of 88%. Unlike previous reports of BM hypocellularity in HLH, our study showed an average BM cellularity of 76%. An HA ≥grade-2, increased histiocytes and atypical lymphocytes, and presence of intact engulfed hematopoietic cells are key morphologic features of HLH. In contrast, HLH mimics often show absent or rare HA, no significant increase of histiocytes and atypical lymphocytes, and degenerated engulfed cells accompanied by cellular debris and hemosiderin pigment. The grade of HA in HLH does not correlate with laboratory findings.

1574 "Inflammatory Abruption" in Second Trimester Deliveries Suggests Cervical Incompetence

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Background: Previous studies have suggested different mechanisms in the pathogenesis between term and preterm clinical abruption. In specific, inflammation has been proposed to be etiologic in placental abruption in the preterm period. The aim of this study was to evaluate the pattern of inflammation and hemorrhage in placental abruptions that occurred in the early second trimester compared to those at term, and to assess clinical correlations.
Design: Placental slides of 103 abruption cases at 14-24 weeks gestation and 118 term abruption cases examined at Brigham and Women's Hospital from 2003 to 2008 were reviewed with respect to location and pattern of hemorrhage. Features of maternal and fetal acute inflammation were evaluated based on standardized classification.
Results: Preterm deliveries had higher rates of premature membrane rupture (41.7% vs. 0.8%, $p<0.001$) and clinical chorioamnionitis (29.1% vs. 4.2%, $p<0.001$). Term deliveries had higher rates of maternal hypertensive disorders (7.6% vs. 1.0%, $p=0.021$) and clinical abruption (79.7% vs. 28.2%, $p<0.001$). Multiple hemorrhagic sites were seen in 91.3% of early second trimester and 39.8% of term abruption cases ($p<0.001$). Any bleeding (retroplacental, retromembranous, subchorionic, intervillous, intravillous) was more common in preterm vs. term placentas ($p<0.001$ except retromembranous, $p=0.005$); retroplacental and subchorionic sites were most common. Inflammation, irrespective of stage, duration, and fetal vs. maternal origin, was more prevalent in the preterm ($p<0.001$). Within preterm, fetal inflammatory responses showed more advanced stage and grade at 20-24 weeks than at 14-19 weeks ($p<0.001$). Only abruption-associated placental infarction was more common at term ($p<0.001$). 29.1% of preterm abruption cases had clinically diagnosed cervical incompetence (CI); these had advanced stage chorioamnionitis relative to preterm deliveries without clinical CI ($p<0.001$). Stillbirths were frequent at preterm (75.7% vs. 4.2%, $p<0.001$); neutrophils were seen in airways and/or intestinal lumens in 43.1% of autopsied preterm fetuses, but none at term.
Conclusions: Amniotic fluid infection is highly associated with placental abruption in second trimester deliveries. We propose the term "inflammatory abruption," to distinguish these cases of inflammation-induced maternal bleeding from abruption due to maternal vascular disorders that occur later in gestation. "Inflammatory abruption" as a pathologic diagnosis raises concern for cervical incompetence.

1575 Histologic Changes in Placentas with Gross Umbilical Cord Abnormalities Correlate with Adverse Perinatal Outcome

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Background: Gross umbilical cord abnormalities predisposing to fetal blood flow restriction have previously been associated with adverse perinatal outcomes; however, their common occurrence in uncomplicated births raises questions regarding their true clinical significance. Using previously established histologic parameters for stillbirth-associated compromise of umbilical blood flow, we set out to evaluate a wide range of gross cord abnormalities and their associated perinatal outcome.
Design: This was a retrospective case-control study, with 297 placentas with grossly abnormal cords and 383 gestational age-matched controls randomly selected from the pathology database. The gross cord abnormalities included excessively long cord, nuchal cord, true knot, and abnormal insertion. Placental slides from each case were reviewed by two pathologists, blinded to the clinical and gross findings. The presence of stasis-associated changes in the placental fetal vasculature, including 1) vascular ectasia, 2) thrombosis, and 3) fetal thrombotic vasculopathy (defined by avascular villi or villi with stromal karyorrhexis), was documented. Results were tabulated along with perinatal outcome data from patients' charts.
Results: Of the cases with single cord abnormalities, nuchal cords and long cords showed 1.5-5 fold higher rates of all stasis-induced histologic changes in the placenta; they also showed 3-8 fold higher rates of adverse perinatal outcome, including stillbirth and growth restriction (IUGR). Cases with multiple cord abnormalities showed 1.5-3 fold higher rates of stasis-induced ectasia and thrombosis, as well as 2-fold increased rate of IUGR. Compared to abnormal cord cases without thrombosis, the odds ratio for adverse outcome in abnormal cord cases with thrombosis was 2.90 (1.36-6.17, 95% confidence interval).
Conclusions: We conclude that stasis-induced changes in the placental fetal vasculature pinpoint the subgroup of gross cord abnormalities associated with adverse perinatal outcome. This study further demonstrates the importance of placental histologic examination, particularly in the setting of poor clinical outcome. Based on this study, we recommend proper sampling of chorionic plate vessels and placental parenchyma in order to identify these histologic changes in the placenta.