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PLATFORM and POSTER PRESENTATIONS

Autopsy

1 Morphological and Molecular Profiling of Pediatric Brain Stem Gliomas.

MA Arnold, S Shandilya, S Galli, JK Killian, M Raffeld, M Tsokos, PS Meltzer, KE Warren, MM Quezado. National Institutes of Health, Bethesda, MD.

Background: Each year, about 2200 children will be diagnosed with a brain tumor, with up to 15% of these tumors localized to the brain stem, where they are uniformly lethal with a variable but typically short survival time. The mean age at diagnosis for primary brain stem tumors is 7 to 9 years, with roughly equal distribution between the sexes. Brain stem gliomas are diffusely infiltrating lesions of both low to high grade morphology. Response to standard treatment, a combination of radiation and chemotherapy regimens, has been disappointing, with minimal if any impact on overall survival. Given the dismal prognosis of these lesions, new therapeutic targets need to be identified. Current research has focused on mechanisms which promote tumor survival by apoptosis resistance, and the identification of "brain tumor stem cells" as potential explanations for resistance to current therapies. Identification of "tumor stem cell" populations in various tumors may allow for their specific eradication with lasting remissions.

Design: We review the morphology of pediatric brain stem gliomas and probe these tumors for chromosomal aberrations by comparative genomic hybridization (CGH). Using immunohistochemistry, we assay brain stem gliomas for the expression of p53, EGFR and Nestin. We also analyze these tumors for mutations in B-RAF.

Results: Our study describes the demographics and clinical features of brain stem gliomas from 13 patients ranging in age at diagnosis from three to 13 years. The tumors we examined are morphologically heterogeneous. We identify many chromosomal aberrations in brain stem glioms by comparative genomic hybridization (CGH), and correlate these findings with the clinical behavior of these tumors. We demonstrate expression of p53, EGFR and the stem cell marker Nestin in a subset of brain stem gliomas. We report the absence of valine to glutamate mutations at residue 600 (V600E) of the B-RAF gene in our cohort of tumors.

Conclusions: Further molecular and immunohistochemical characterization is ongoing, and our findings may identify genetic alterations in these tumors that may represent the molecular hallmarks of these lesions, genetic markers of prognosis, and potential targets for future therapies.

2 Autopsy Findings in Sarcoma Patients Treated by a Multidisciplinary Group in the Current Era.

SS Bhusnurmath, C Fligner, BL Hoch. University of Washington Medical Center, Seattle.

Background: Autopsy remains a valuable tool in understanding the course of disease. Autopsy studies on sarcoma patients have consisted of case reports or large series focused on specific subtypes of sarcoma published prior to more recent therapy protocols. We reviewed a series of autopsies on sarcoma patients often treated with aggressive therapy by a multidisciplinary sarcoma group in the current era.

Design: The institutional files from 1989-2010 were searched for autopsy cases with a diagnosis of sarcoma. 26 cases were identified. Autopsy reports and routine H&E slides were reviewed to confirm the diagnosis and determine the extent of disease, complications, cause of death, length of survival, and comorbidities. Comparison between clinical findings and autopsy findings was also performed.

Results: Patients ranged in age from 20-85 (mean 55) yrs. There were 18 males and 8 females. Sarcoma types included 6 leiomyosarcomas,6 angiosarcomas,3 pleomorphic undifferentiated sarcomas, 2 GISTs, and 1 case each of dedifferentiated liposarcoma, well differentiated liposarcoma, endometrial stromal sarcoma ,Ewing sarcoma, chondrosarcoma, extraskeletal osteosarcoma, MPNST, myxoid liposarcoma and histiocytic sarcoma. The diagnosis was revised at autopsy in 3 cases. The underlying cause of death was sarcoma in all but 2 cases. Immediate causes of death were pneumonia (7), metastatic disease (6), exsanguination (3), local disease (2), coronary artery disease (1), stroke (1), and pulmonary embolus (1). In 5 cases the immediate cause of death was iatrogenic including cardiac arrythmia from SVC stent placement, Adriamycin related cardiomyopathy, renal failure following aorta reconstruction, chemotherapy related lung injury, and radiation induced sarcoma. The most common complications included infections, DVT, pulmonary embolus, and cytopenias. Metastases were present in 25 patients with lung, liver and bowel being most common. In 20 cases the extent of sarcoma at autopsy exceeded what was reported clinically. The median survival time was 6.3 months.

Conclusions: Autopsies are performed on sarcoma patients due to unusual subtype, unexpected clinical course, or rapid demise. Pneumonia, metastatic disease and iatrogenic complications are the most common immediate causes of death. Extent of sarcoma at autopsy commonly exceeds clinically documented disease. Autopsy can allow for more definitive classification of sarcoma in some cases. A larger number of autopsies should be performed on sarcoma patients to better understand the course of disease and complications in the current era.

3 10 Year Autopsy Experience at a Tertiary Care Hospital.

BY Bradshaw, TP Chaba. University of Alberta, Edmonton, Canada.

Background: The autopsy has long been accepted as the gold standard of diagnosis, playing a valuable role in both clinical accuracy and medical education. The error rates shown in 1980s autopsy series have remained relatively constant, despite speculation that the advent of modern imaging techniques would improve antemortem diagnostic accuracy. The aims of this study were to examine ten years of autopsy data at a tertiary care university hospital, looking at autopsy rates, diagnostic accuracy, and the potential influence of modern imaging techniques on error rates.

Design: Consecutive autopsy reports performed at the University of Alberta Hospital during three years of a ten-year period were obtained, from January 1 to December 31 of 1997, 2003 and 2006. Pediatric and neurologic-only autopsies were excluded. The data were analyzed to determine the numbers of autopsies performed, the hospital autopsy rate, the major error and class I error rates, and the concordance between radiologic and autopsy diagnoses.

Results: The data showed that hospital autopsy rates declined from 11.7% to 5.6%. The most common diagnostic categories causing death in 1997 and 2003 included cardiovascular (33%) and infection (20.4%). In 2006 a shift was seen, with malignancy accounting for the highest proportion of deaths (29.2%). The most common anatomic cause of death was coronary artery disease in 1997 and 2003, with a shift to gastrointestinal and lung malignancies in 2006. The overall concordance rate increased from 39.7% in 1997 to 45.9% in 2006, while the overall discrepancy rate decreased from 60.3% in 1997 to 54.1% in 2006. The major error rate did not change throughout the study period, but the class I error rate decreased from 13.1% in 1997 to 7.3% in 2006. The most common class I errors were myocardial infarction/coronary artery disease (29.6%), followed by pneumonia and pulmonary thromboembolism. Factors such as age, sex, length of hospital stay, as well as antemortem radiologic investigations had no impact on major error rates.

Conclusions: The autopsy data show that the major error, class I error rates and overall discrepancy rates are similar to those previously described in the literature. They have remained relatively stable over a ten year period, and do not seem to have been changed by the use of ante mortem radiologic investigations. This study supports the ongoing belief that continued performance of the hospital autopsy is important with respect to clinical accuracy and medical education, as there remains a significant rate of diagnostic error despite the use of modern imaging techniques.

4 Results from a Specialist Cardiac Pathology Service for Sudden Cardiac Death in the United Kingdom (UK).

SV de Noronha, K Ogo, J Wells, MN Sheppard. Imperial College, London, United Kingdom; Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom.

Background: Sudden, unexplained death is usually due to cardiac disease and its incidence is unknown in the UK. A unique fast track cardiac pathology service, the CRY Centre for Cardiac Pathology, for sudden cardiac death (SCD) in the UK was launched in March 2007 with the generous support of a family who experienced sudden death in two generations. This service was established with the aim of offering a free specialist cardiac pathology diagnosis quickly (two week turn around) to pathologists nationwide.

Design: A prospective non-case control observational study.

Results: A total of 726 cases of SCD were referred from March 2007 to December 2009 consisting predominately of males (60%), median age 31 years. Most deaths took place at home, at rest (56%) but 16% occurred during exertion. Figure 1 shows the main cardiac diagnoses including normal hearts (n=337) (suggesting channelopathy), cardiomyopathy (n=212) and coronary artery pathology (n=71). In the cardiomyopathy group idiopathic left ventricular hypertrophy was most common (n=98), followed by

hypertrophic cardiomyopathy (n=41) and arrhythmogenic ventricular cardiomyopathy (ARVC) (n=30). When comparing the referring pathologist's opinion with ours, in a sample of 200 cases, we found that 27% of the cardiac causes were mismatched and the major discrepancy was an overdiagnosis in ARVC.

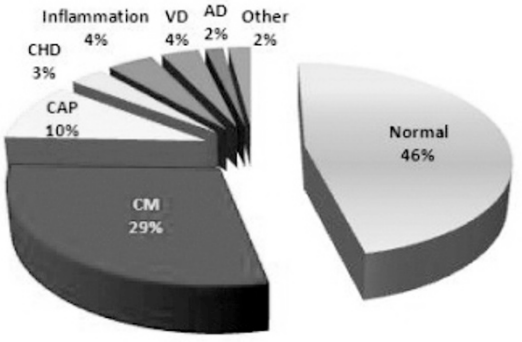


Figure 1. SCD Diagnoses

Abbreviations: AD: aortic disease, CAP: coronary artery pathology, CHD: congenital heart disease, CM: cardiomyopathy, VD: valve disease.

Conclusions: This large prospective study highlights the importance of inherited cardiac disease as a cause of SCD as at least 75% of our referrals are of potentially genetic origin. Our service is important as families are becoming increasingly aware of SCD and wish to establish a specific cardiac cause of death quickly to ensure an early cardiological screening of the remaining family members.

5 Sarcoidosis: Epidemiologic Profile and Autopsy Findings of 22 Cases.

NC Fernandez, R Smith, F Lucas, QJ Zhai. University of Cincinnati, OH; Greater Cincinnati Pathologists, Inc, OH.

Background: Sarcoidosis, a multisystem disorder of unknown cause affecting young and middle-aged adults, often presents with bilateral hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. Other organs may also be involved. The diagnosis is one of exclusion, established when clinicoradiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas. We analyzed the clinical records and autopsy reports of patients seen at a teaching hospital to develop a epidemiologic profile of our population.

Design: 1106 consecutive autopsy cases from January 1st 1999 to July 31st 2010 were reviewed, and decedents with antemortem or postmortem diagnosis of sarcoidosis were included in the cohort. Patients were classified by gender, age, autopsy findings and concomitant conditions.

Results: The male: female ratio was 1:1.The mean age at the time of death was 49.09 years for males and 47.72 years for females. 18 patients were African-American and 4 were Caucasian. Diagnosis of sarcoidosis was antemortem in 13 cases and postmortem in 9. 2 of the cases did not have histological evidence of sarcoidosis on autopsy. The organs involved by the disease in the remaining 20 cases are listed in table 1.

Organs involved by sarcoidosis

Organ	Number of cases
Lungs	15 / 20
Lymph nodes	12 / 20
Heart	8 / 20
Liver	7 / 20
Bone marrow	4 / 20
Spleen	3 / 20
Kidney	2 / 20
Gastrointestinal tract	1 / 20
Central nervous system	1 / 20
Pancreas	1 / 20

Medical history was available for 21 of the 22 cases and concomitant conditions are listed in table 2.

Concomitant conditions

Diagnosis	Cases
Hypertension	14 / 21
Diabetes	11 / 21
Asthma	8 / 21
Kidney disease	8 / 21
Liver disease	4 / 21

10 patients had hypertension and diabetes and 5 patients had hypertension, diabetes and asthma. Sarcoidosis was the main contributor to death in 9 cases. Cardiac sarcoidosis was present in 5 of those.

Conclusions: Race and gender distribution of this cohort is similar to that reported in the literature, with predominance of African American and 1:1 male:female ratio. Airway hypereactivity is reported in up to 20% of sarcoidosis cases. In our series it was present in 40% .Cardiac sarcoidosis is a rare manifestation, symptomatic in 5% of patients. In our series there was myocardial involvement in 40% of cases and accounted for 55% of deaths directly caused by sarcoidosis. This observation underscores the importance of appropiate sampling of the heart to avoid failure to report this finding.

6 The Incidence of Liver Disease Diagnosed by Perinatal Autopsy.

L Griffits, SH Pepkowitz, SA Geller. Cedars-Sinai Medical Center, Los Angeles, CA.

Background: Aside from hypoxic injury significant hepatic disease is unusual in neonates, although the potential etiologies are numerous. Moreover, in ill neonates the presence of specific liver disease may be unsuspected because of multi-organ compromise and, even if overt, often not amenable to liver biopsy for definitive diagnosis. To better understand the frequencies of various hepatic diagnoses we reviewed 20 years of perinatal autopsies from one institution focusing on hepatobiliary findings.

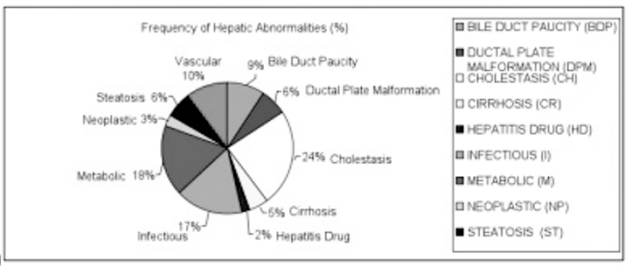
Design: Records of 596 perinatal autopsies performed at our tertiary care institution from 1990 through 2010 were reviewed for any "final diagnosis" of hepatobiliary disease: we identified 84 cases (14%). For these cases the clinical history was reviewed and relevant slides were re-examined for bile duct anomalies, ductal plate abnormalities, bile duct paucity, cholangiopathy, cholestasis, hepatitis or liver-based infection, steatosis, vascular abnormalities, hematopoietic abnormalities or neoplasia.

Results: 1. In 37 of the 84 cases only one type of liver disease was diagnosed.

Diagnosis # of cases

Metabolic disease: 2
Steatosis: 3
Bile duct paucity: 5
Ductal plate malformation: 5
Infection: 6
Cholestasis: 8
Vascular anomalies: 8

2. In 47 of the 84 cases multiple hepatic diagnoses were present. The total frequencies of the categories (including single and multiple concurrent diagnoses) are represented by the pie-chart below.



Conclusions: In spite of advanced imaging techniques and other diagnostic modalities, autopsy studies in adults not infrequently uncover additional significant conditions that could have altered therapy and outcome had they been recognized earlier. Our study suggests that the perinatal autopsy also recognizes hepatobiliary conditions that are not always recognized pre-mortem and, additionally, may significantly impact genetic counseling of family members.

7 Fetal & Placental Findings in Stillbirth Associated with Pregnancies Complicated by Intrahepatic Cholestasis.

M He, S Kostadinov, H Pinar. Women & Infants Hospital/Brown University Medical School, Providence, RI.

Background: Intrahepatic cholestasis of pregnancy (ICP) is a condition associated with high rate of unpredictable stillbirth. The pathogenesis of IUFD is poorly understood and there is no data on postmortem examination in the literature. Here, we present clinical, laboratory and histopathological data on a single-institution series of stillbirth associated with ICP.

Design: This is a retrospective study by searching the archives for postmortem examinations from October 2006 to September 2010 with keyword "cholestasis". Clinical information including prenatal history, maternal peak bile acid level, medications, and postmortem examination findings were extracted from the Hospital Health Information System.

Results: Eighty cases of ICP were identified with 4 with stillbirth (4/80, 5%). Clinical information and pathology findings are summarized in table 1:

Case No.	Gestational Age (wks)	OB & Prenatal History	Peak Bile Acid Level (mcmol/L)	Placental findings	Fetal gender	Postmortem findings
1	30	G5P0404, cholecystectomy, pruritus. On Delalutin & Ursodiol	175	SGA, meconium, erythroblastosis, uneven villous maturity	M	LGA, perinatal stress
2	38	G5P0202, incompetent cervix, nephrolithiasis, cholecystectomy. On Delalutin	109	SGA, meconium, acute CA	F	Perinatal stress, grade I maceration, body cavity fluid including pericardial effusions
3	36.5	G1P0, on Ursodiol	109	AGA, meconium, Intervillous thrombi	M	Perinatal stress, body cavity fluid including pericardial effusions, hepatomegaly
4	38	G3P0020, generalized pruritus	28	AGA, meconium, acute subchorionitis, villous edema and Tenney-Parker changes	N/A	N/A

SGA, small for gestational age. AGA, appropriate for gestational age. CA, chorioamnionitis

In stillbirth associated with ICP, there were evidence of intrauterine fetal distress. The associated peak bile acid values varied significantly, including less than 40 mcmol/L. In two of the three fetal examinations, body cavity fluid, esp., pericardial effusions are present. These could be sign of impending hydrops, an indicator of possible cardiac dysfunction.

Conclusions: This study suggested that maternal bile acid level is not a reliable indicator of potential intrauterine fetal demise. The fetal findings may correlate with one *in vitro* study that increased fetal serum bile acid level could impair fetal cardiomyocyte function. Our result indicated the importance to study the effects of bile acid on fetal tissue, in addition to current emphasis on placenta.

8 Body Mass Index Alone Does Not Predict the Amount of Steatosis in Livers of Patients without Alcoholism or Viral Hepatitis: A Retrospective Autopsy Study.

JF Hechtman, AC Jordan, MI Fiel, IA Scordi-Bello. Mount Sinai School of Medicine, New York, NY.

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver disorders in western countries. Moderate to severe steatosis is a contraindication for living-donor liver transplantation. In living-related donation, >15% steatosis is a contraindication. Studies using ultrasonography to assess NAFLD in the general population report that up to 94% of obese individuals have NAFLD.

Design: The purpose of this study was to determine whether body mass index (BMI) alone, in the absence of alcohol or viral disease can predict the severity of steatosis. Bland hepatic steatosis (BHS) and steatohepatitis (SH) were assessed histologically in 72 autopsy cases. Steatosis was graded as 0 (<5%), 1 (up to 33%), 2 (up to 66%) or 3 (>66%). Steatohepatitis was graded as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). BMI, subcutaneous fat thickness, heart weight, and liver weight were obtained from autopsy reports. Admission alanine aminotransferase levels (ALT) and diagnoses of diabetes mellitus were obtained from medical charts. Exclusion criteria included diagnoses of viral hepatitis and/or alcoholism.

Results: We studied a total of 72 cases. 62.5% were categorized as obese (BMI>=30) and 37.5% were non-obese (BMI<30). The age range was 21-89 years. 37.5% were male and 62.5% were female. 47.2% had a clinical diagnosis of type II diabetes. Statistical analysis revealed that there was a positive correlation between BMI and liver weight, subcutaneous fat, and heart weight ($p<0.05$). There was no correlation between BMI and BHS. In patients with BMI<30, 88.9% had no or mild BHS and 11.1% had moderate or severe BHS. In obese patients with BMI≥30, 82.2% had no or mild BHS and 17.8% had moderate or severe BHS. Overall, 11/72 patients had 5% to 33% steatosis, and 11/72 patients had >33% steatosis. Although a higher percentage of obese patients exhibited moderate to severe steatosis, this increase was not statistically significant ($p=0.450$). There was no correlation between BMI and ALT. 10/72 patients exhibited mild, 1/72 moderate and 2/72 severe SH. Both patients with severe SH were obese.

Conclusions: BMI alone is not a reliable predictor of the degree of steatosis. The majority of obese patients in our study had only mild steatosis. Just as many non-obese patients had moderate to severe steatosis. While the numbers are small and the study is retrospective, it highlights the complexity of NAFLD and the inability of one single variant to predict its severity. Liver biopsy remains the gold standard for assessing any liver for donation.

9 The Role of Notch Signaling Pathway in Human Fetal Pancreas and Pancreatic Cancer.

H Hu, L Zhou, A Awadallah, W Xin. University Hospitals of Cleveland, Case Medical Center, OH; Case Western Reserve University, Cleveland, OH.

Background: Notch signaling pathway plays an important role in the pancreatic embryogenesis mainly by animal model studies. There are limited studies of notch pathway on the development of human pancreas. Here we examine the expression of Notch1, the main notch receptor in the pancreas, in human fetal pancreas obtained from autopsy.

Currently targeting notch signaling pathway with γ-secretase inhibitor has been extensively studied as a treatment option for patients with pancreatic ductal carcinoma since notch pathway activation is an early event in the pancreatic tumorigenesis. The expression of Hes1 is one of the indicators for Notch activation. Here we compare Notch1 expression in the human pancreatic ductal adenocarcinoma and its precursors and explore the role of notch pathway in the pancreatic ductal adenocarcinoma.

Design: 43 autopsy cases of normal fetal pancreas and 66 surgical cases of pancreatic ductal adenocarcinoma were studies. Immunohistochemistry was performed using antibodies specific for Notch1 and Hes1.

Results: Notch 1 expression is identified in acinar cells and centroacinar cells, but not ductal cells or endocrine cells. The level of Notch1 expression increases during pancreatic maturation and reaches plateau right after birth. No expression of Notch1 is identified in acinar to ductal metaplasia and PanIN1-3. Notch1 reactivation is identified in 33% cases of pancreatic ductal adenocarcinoma. The notch activation in the cancer is confirmed by Hes1 expression. Notch1 expression in pancreatic ductal adenocarcinoma shows poorer differentiation comparing to Notch1 negative cancers.

Notch1 expression in pancreatic ductal adenocarcinoma by studying 66 surgical cases

	Positivity (%)	Expression Pattern
Normal pancreas	100	diffuse membrane
Chronic pancreatitis	100	variable, membrane
Acinar to ductal metaplasia	0	NA
PanIN 1	0	NA
PanIN 2	0	NA
PanIN 3	0	NA
Ductal adenocarcinoma	33	variable, luminal

Conclusions: Notch signaling pathway plays an important role in both pancreatic embryogenesis and carcinogenesis. Notch signaling pathway is inactivated in non-neoplastic ductal system and PanIN 1-3. However, 33% cases of pancreatic ductal adenocarcinoma show reactivation. Clinical treatment with notch signaling inhibitor including γ-secretase inhibitor should be selectively used for patients diagnosed with pancreatic neoplasm.

10 Correlation between Body Mass Index and Atherosclerosis in Coronary Arteries and Aorta: A Retrospective Autopsy Study.

AC Jordan, JF Hechtman, IA Scordi-Bello. The Mount Sinai Medical Center, New York, NY.

Background: Obesity has been considered a risk factor for coronary artery disease and mortality in men in large prospective studies. In those studies, "abdominal type" fat distribution was considered an important risk factor; however, the mortality data used was from death certificates and not autopsy data. The purpose of this retrospective autopsy study was to determine if body mass index (BMI) alone is predictive of coronary atherosclerosis (CA) and aortic atherosclerosis (AA).

Design: We retrospectively assessed CA and AA following post-mortem exam of 61 patients. Patient age, race, weight, and medical history were obtained from the medical record. Patient height, heart weight, and subcutaneous fat thickness were obtained from the autopsy report. Two pathologists examined the left anterior descending, circumflex and right coronary arteries and the thoracic, abdominal and infrarenal aorta. Atherosclerosis was graded as: 0 = none, 1 = mild (< 25% coronary stenosis; rare fatty streaks or fibrous plaques in the aorta), 2 = moderate (25-70% coronary stenosis; numerous fatty streaks, fibrous plaques or calcified lesions in the aorta) and 3 = severe (> 70% coronary stenosis; numerous/large calcified lesions or complicated, ulcerated lesions in the aorta). The scores of the three coronary arteries were added to give a possible total score of 0-9. The scores of the three segments of aorta were added to give a possible total score of 0-9.

Results: Sixty-one adult cases were examined. The age range was 20-97 years; 45.9% male and 54.1% female; 68.9% BMI < 30 kg/m^2 and 31.1% BMI >= 30 kg/m^2. Regression analysis showed a positive correlation between BMI and heart weight ($p < 0.005$) and between BMI and subcutaneous fat thickness ($p < 0.005$). There was no correlation between BMI and total CA ($p = .235$). In patients with BMI < 30, 57.1% had mild, 28.6% had moderate and 14% had severe total CA while in the obese group with BMI >= 30, 68.4% had mild, 21.1% had moderate and 10% had severe total CA. There was no correlation between BMI and thoracic, abdominal, infrarenal or total AA. In fact, of thoracic aortas with no atherosclerosis, 40% were non-obese and 60% were obese while none of those with severe atherosclerosis were obese (0%) and 100% were non-obese. There was a positive correlation between total CA and total AA, independent of BMI ($p<0.005$).

Conclusions: Our study suggests that obesity in and of itself is not predictive of pathologic coronary and/or aortic atherosclerosis and confirms that atherosclerosis is a complex systemic disease affected by many variables.

11 Impact of Intrauterine Retention on Determining Cause of Death in Stillborns.

R Li, OM Faye-Petersen, MP Steinkampf, SD Reilly. University of Alabama at Birmingham; Alabama Fertility Specialists, Birmingham.

Background: Intrauterine fetal demise is an emotionally devastating event for women and their doctors. The perinatal autopsy is an important tool in determining the cause of fetal death (COD). Either expectant management or induction of labor is considered an appropriate option under these circumstances, but how the choice of patient management affects the accuracy of the autopsy is not known. The purpose of this study was to evaluate the effect of intrauterine retention (IUR) on pathologists' abilities to determine COD from the perinatal autopsy.

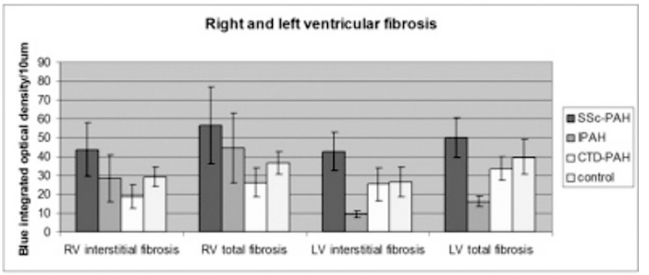
Design: This was a review of all cases of stillbirth (≥20 wk gestational age) submitted for autopsy at a tertiary care university hospital between 1/1/1992 and 5/5/2010. COD was determined by clinical history, additional laboratory testing as indicated, and autopsy findings of the fetus and placenta. The interval between fetal demise and delivery was determined both by history and by evaluating the characteristic histologic changes in fetal organs and placenta according to the criteria of Genest and colleagues (ObstetGynecol.1992;80:575-592). Statistical analyses were performed using contingency table analysis and parametric or nonparametric analysis of variance as appropriate.
Results: A total of 404 cases were reviewed. A placenta was submitted in 92% of cases. The mean maternal age was 24.4 yr (range 14 to 44 yr). The stated maternal race was Asian 1%, Black 68%, Hispanic 4%, White 27%. The mean gestational age at demise was 29.9 weeks (range 20 to 43 weeks). A vaginal delivery was performed in 96% of cases. Fetal sex was male in 55% of cases and undetermined in 1 case. No COD could be determined in 22% of cases. The IUR period was specified in all but one autopsy report, with a mean of 5.9 days (range 1 to 112 days, median 2.25 days). The mean IUR time in cases with determinations of COD was 4.0 days, compared to 12.4 days in cases for which no COD could be determined (P<0.0001). A COD could be determined in 89% of cases in which IUR time was less than 7 days, but in only 46% of cases with IUR time ≥7days (P<0.0001). The differences persisted when cases of placental abruption, acute chorioamnionitis, or intrapartum demise were excluded from the analysis.
Conclusions: Prolonged intrauterine retention (≥7d) after fetal demise is associated with decreased ability to identify the cause of death.

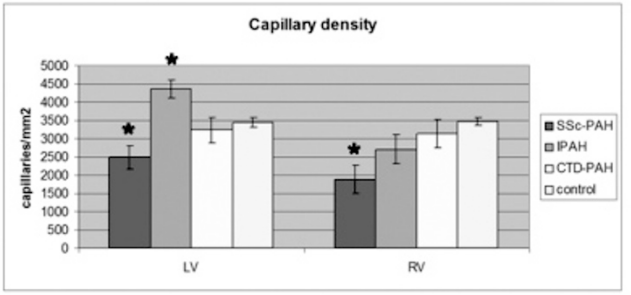
12 Exactly How Does Lung Cancer Kill Patients?

L Nichols, R Saunders, F Knollmann. University of Pittsburgh Medical Center, PA.
Background: Little is published identifying or quantifying the causes of death of lung cancer patients. Autopsies of lung cancer patients are ideally suited to shed light on the mechanisms of death of these patients.
Design: 100 autopsies of patients who died of lung cancer from 1990 through 2009 were analyzed to tabulate and analyze the causes of death.
Results: 62 of the patients were male and 38 female. 82 were white, 17 black and 1 east Asian. The average age was 66 (range 33-88). 47 of the cancers were adenocarcinomas, 26 squamous cell carcinomas, 18 small cell carcinomas, 8 large cell undifferentiated carcinomas and 1 mucoepidermoid carcinoma. Tumor burden was judged to be the immediate cause of death in 34 cases, including 24 cases of extensive metastases, 7 cases of lung tumor burden causing respiratory failure and 3 cases of local invasion (1 invading heart, 1 invading nervous system, 1 invading pulmonary artery and vena cava). Infection was the immediate cause of death of 21 patients, including 16 pneumonias. Complications of metastatic or extrapulmonary invasive disease were the immediate cause of death in 18 cases, including 9 involving the heart, 4 liver and 3 brain. Other immediate causes of death were pulmonary hemorrhage (12 cases), pulmonary embolism (9 cases, 2 tumor emboli) and pulmonary diffuse alveolar damage (6 cases). From a functional (pathophysiologic) perspective, respiratory failure, usually due to a combination of causes including emphysema, obstructive lung disease, pneumonia, hemorrhage, embolism, pneumonectomy, lobectomy and lung injury in addition to tumor could be regarded as the immediate cause of death in 37 cases. Almost all 100 patients had contributing causes of death and lung cancer was the underlying cause of their deaths. Patients who died with, but not of lung cancer (with lung cancer only a contributing cause of death), not included in the main analysis of this study, almost all died of atherosclerotic cardiovascular disease or smoking-related disease. 40 patients received no treatment, 14 because the lung cancer was not diagnosed antemortem. Rare mechanisms of death included paraneoplastic Lambert-Eaton syndrome, thrombosis of pulmonary artery and vena cava stents and platypnea-orthodeoxia syndrome due to tumor emboli with a patent foramen ovale.
Conclusions: The multiplicity and complexity of the causes of death of lung cancer patients pose challenges for efforts to extend and enhance the quality of their lives, but knowing the specific causes is important for these efforts.

13 Cardiac Findings in Patients with Systemic Sclerosis Associated Pulmonary Arterial Hypertension.

JE Pogoriler, SL Archer, S Rich, L Piao, AN Husain. University of Chicago Medical Center, IL.
Background: Isolated pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc-PAH) has a poor prognosis. Survival is significantly worse than for patients with idiopathic PAH (IPAH). We previously found that SSc-PAH patients had a greater involvement of pulmonary arterioles and capillaries compared to IPAH patients and patients with other connective tissue disease-associated PAH (CTD-PAH). The poor prognosis of SSc-PAH could reflect either these pulmonary vascular factors or a relative inability of the right ventricle to adapt to increased pressures. This could be due to increased cardiac fibrosis or altered vascularity in SSc.
Design: We reviewed the cardiac histology and gross descriptions from 6 autopsy cases of SSc-PAH, 5 cases of IPAH, 5 cases of PAH associated with other types of connective tissue disease (CTD-PAH), and 8 controls. We quantified left and right ventricular interstitial and total fibrosis using a trichrome stain with an automated imaging system. We constructed a tissue microarray and quantified capillary density following immunohistochemistry for CD31.
Results: There was no significant difference among heart weights or right ventricular thickness among PAH patients of different etiologies, but all groups were heavier and thicker than controls. One SSc-PAH case had focal thickening of the intramyocardial vessel walls and patchy subendocardial fibrosis, but there were no other signs of cardiac involvement by systemic sclerosis. SSc-PAH patients tended to have more fibrosis in both the left and right ventricles, but the difference was not significant. Unlike IPAH and CTD-PAH patients, SSc-PAH patients had a significantly lower capillary density in both the right and left ventricles than control hearts (p<0.05). Unexpectedly, IPAH patients had a significantly higher capillary density in the left ventricle compared to all other groups.





Conclusions: We found no convincing evidence that patients with SSc-PAH have increased fibrosis relative to other types of PAH to explain poor survival. However, there were differences noted in capillary density among the groups which could affect ventricular function. These findings warrant further studies.

14 The Importance of Placental Examination in Stillborn and Neonatal Autopsies.

AS Shahab, H Nassar, Y Ahmed, PJ Kowalski. St. John Hospital and Medical Center, Detroit, MI.
Background: Fetal death is quite a devastating loss to families. Many fetal deaths are unidentifiable. Perhaps gross and microscopic examination of the placenta can play a more crucial role in the understanding the etiology of fetal demise in such cases. Consequently, the pathologist can bring some closure to these families.
Design: A retrospective cohort study concerning all stillbirth and neonatal autopsies over a period of 10 years (January 2000-January 2010). We selected only cases with corresponding placentas.
Results: There were 88 autopsies satisfying all criteria, 65 still borns and 23 liveborns. We first reviewed the diagnostic findings of the autopsies which were grouped into two categories: A diagnostic category which includes 33 cases (37.5%) with pertinent gross anomalies involving mainly brain, heart, lungs, or kidneys and findings consistent with fetal stress and prematurity, such as renal and adrenal hemorrhages, hyaline membrane disease, or intracranial hemorrhage. The second includes nondiagnostic category of 55 cases (62.5%) showing either normal findings or advanced autolysis. By correlating the corresponding placentas, it was determined that 62 cases (70.5%) had pertinent findings like chorioamnionitis or abruption and retroplacental hematomas. This important correlation of autopsy and placental examination significantly increased the diagnostic yield from 37.5% to 70.5%.
Conclusions: Even though the autopsy is a key diagnostic tool in unexplained fetal demise and neonatal deaths, our study illustrates the importance of correlating placental examination along with the autopsy findings. It proves that it can enhance the pathologist's diagnostic ability in these cases.

15 Lack of Correlation between Coronary Plaque Burden and Heart Weight at Forensic Autopsy.

J Shields, L Li, DR Fowler, Y Zhang, AP Burke. University of Maryland, Baltimore; Maryland Office of the Chief Medical Examiner, Baltimore; University of Maryland School of Medicine, Baltimore.
Background: It is unclear if extent of coronary atherosclerosis is associated with increase in heart muscle mass.
Design: We retrospectively reviewed autopsy reports of sudden coronary deaths occurring in a statewide medical examiner system over a one-year period. Cardiomegaly was assessed by body weight and height, and given a score of 0-4 based on amount above the upper limit of normal range. Hypertension was assessed by history or renal vasculature findings. Coronary disease was quantitated as number of epicardial arteries (left main, left anterior descending, left circumflex and right coronary and their major branches) with ≥ 75% cross sectional luminal narrowing, for a score of 1-4.
Results: There were 178 men (50±11 years) and 58 women (57± 18 years). There were 100 hearts with 1-vesel disease (66 men, 34 women), 77 with 2 vessel disease (59 men, 18 women), and 59 with three- or four vessel disease (53, men, 6 women). Extent of disease was less in women than men (p=.004). Hypertension was present in 36% of men, and 45% of women. Body mass index was 30 ± 6 in men, and 27 ± 6 in women. Healed infarcts were present in 14% of women and 28% of men. Cardiomegaly was present in 50% of women, and 69% of men. By univariate analysis, cardiomegaly score increased with number of stenosed arteries (p=.02) as well as % of hearts with cardiomegaly (p=.004), in patients without hypertension. However, by multivariate

analysis, only age (p=.008), body mass index (p<.0001) and presence of healed infarct (p=.06) were associated with cardiomegaly score, extent of coronary disease showing no correlation (p=0.9).
Conclusions: There is no significant correlation between extent of coronary atherosclerosis and cardiac hypertrophy independent of age and body mass index in sudden coronary deaths. These data do not support a causative association between chronic ischemia and cardiomegaly.

16 Nonspecific Cardiomyopathy: A Common Cause of Death with a Need for Standardization of Terminology.

J Shields, L Li, DR Fowler, Y Zhang, AP Burke. University of Maryland, Baltimore; Maryland Office of the Chief Medical Examiner, Baltimore; University of Maryland School of Medicine, Baltimore.
Background: The terminology and classification of sudden cardiac deaths in patients with cardiomegaly as the primary cause of death have not been clarified.
Design: A retrospective review of autopsy records from a single calendar year at a state-wide medical examiner's office was performed. Cases of sudden cardiac deaths were retained for study. Causes of death and cardiac findings were tabulated, and cases with potential noncardiac causes, such as drug and alcohol related deaths, were excluded. Cases with coronary atherosclerotic disease (≥1 vessel with ≥75% luminal area narrowing) were excluded. Cardiomegaly was determined based on body height and weight; mild cardiomegaly was defined as <50 grams above the 95% upper limit; moderate: 50-99 grams; marked: 100-200 grams; and massive: >200 grams above the limit, respectively. The incidence, demographics and terminology applied for these deaths was analyzed.
Results: Among 484 sudden cardiac deaths, 241 deaths (50%) had severe atherosclerosis, 41 arrhythmia/ sudden adult death syndrome (8%), 15 valvular disease (3%), 19 inflammatory or specific cardiomyopathy (4%) and 5 miscellaneous causes (1%). 161 deaths were due to nonspecific cardiomyopathy (NSC) (33%). Hypertrophic cardiomyopathy was excluded based on the lack of septal asymmetry and myofiber disarray. Of NSC cases, the mean age was 46 ± 12 years; there were 104 males and 57 females; 45% were African American. A history of hypertension was present in 66 cases (47%). The mean body mass index (BMI) was 33.5 ± 10.6. The mean heart weight was 572 ± 150g. Twelve percent of decedents had a remote history of alcohol abuse. Twenty-seven percent of the nonspecific cardiomyopathy deaths were witnessed and 1.2% were exertion related deaths. The autopsy reports listed a variety of terms, including left ventricular hypertrophy, arrhythmia associated with cardiomegaly, dilated cardiomegaly, hypertensive cardiovascular disease, and nonischemic cardiomyopathy.
Conclusions: Approximately one third of sudden cardiac deaths are secondary to nonspecific cardiomyopathy; however, a uniform nomenclature for the causes of death in these cases is lacking. The term nonspecific cardiomyopathy is recommended for use in such cases, with risk factors such as hypertension, obesity and alcoholism listed as contributing factors.

17 Integration of Autopsy Pathology and Genetics in Hunter Syndrome (MPSII).

LD Wood, MK Halushka, FB Askin, LC Racusen, RA Anders, B Baskin, PN Ray, T Van Kuppevelt, RG Wismans, BJ Crain, MR Natowicz, GS Bova. Johns Hopkins University School of Medicine, Baltimore, MD; The Hospital for Sick Children, Toronto, ON, Canada; Radboud University, Nijmegen Medical Centre, Netherlands; Cleveland Clinic, OH.
Background: Hunter syndrome (MPSII), a rare X-linked lysosomal storage disorder caused by germ-line mutations in the iduronate-2-sulfatase (*IDS*) gene, is a mucopolysaccharidosis characterized by abnormal accumulation of glycosaminoglycans (GAGs) in multiple organs. Although the clinical syndrome of MPSII is well described, systematic anatomic studies of its pathology are limited, and studies integrating gross and microscopic pathology with specific mutations have not been reported. Insights from these natural human mutations affecting GAG degradation could improve our understanding of the role of GAGs in health and disease.
Design: We performed comprehensive gross and microscopic analysis for 2 autopsy subjects with MPSII. Tissues were examined using H&E staining, colloidal iron staining, and a novel antibody specific for dermatan sulfate. We also performed DNA sequencing on all coding exons of the *IDS* gene in formalin-fixed paraffin-embedded lymphoid tissue from each patient.
Results: DNA sequencing of the *IDS* gene revealed different pathogenic mutations in each patient: one novel single-base deletion in exon 6 creating an in-frame stop codon (c.817delC, p.Arg273fsX) and one previously reported disease-causing missense mutation in exon 3 (c.253G>A, p.Ala85Thr). Gross examination of tissues at autopsy confirmed previously reported anatomic anomalies and identified novel findings, including coronary artery occlusion (not previously reported in MPSII) and choroid plexus fibrosis (not previously reported in any mucopolysaccharidosis). Microscopic examination revealed that abnormal vacuolated cells containing undegraded GAGs were present in multiple organs, including the heart, blood vessels, lungs, liver, kidney, and brain.
Conclusions: This study is the first to integrate systematic autopsy examination with specific mutations in MPSII, highlighting the power of genotype-phenotype correlation in the understanding of the pathogenesis of genetic disease. Moreover, we extend the current notion of genotype-phenotype analysis beyond clinical syndrome to include correlation of gross and microscopic pathology with specific mutations. Expansion of the methods used in this study to additional cases of MPSII could greatly enhance our understanding of the inherited disorders of GAG metabolism and GAG biology more generally.

Bone & Soft Tissue

18 Expression of Therapeutically Relevant Molecules in Ewing's Sarcoma Family Tumors.

A Ahmed, J Whiting, B Pawel. Children's Mercy Hospital, Kansas City, MO; Children's Hospital of Philadelphia, PA.
Background: Ewing sarcoma family tumor (EFT) is an aggressive malignant tumor of bone and soft tissue in children and adolescents. Modern treatment regimens are effective in localized disease. Metastasis occurs in 20-25% of cases and results in mortality in 80% of patients. New insight has led to identification of mTOR, AKt, VEGF and NF-kappa B as important kinases and transcription factors that regulate the proliferation of EFT tumor cells in vitro. BRAF is another kinase molecule that is over-expressed in numerous cancers and has not been previously studied in EFT.
Design: 72 cases with established diagnosis of EFT were selected. Survival data was available in 50 cases, classified as as no evidence of disease (NED), alive with disease (AED) or died of disease (DOD). Formalin-fixed tumor sections were stained with antibodies against phosphorylated mTOR, AKT, BRAF, VEGF and NF-kappa B proteins. Stained sections were analyzed and graded for extent (percentage of stained cells) and strength of staining (negative [0], weak [1] or strong [2]). A composite score (from 0 to 200) was calculated by multiplying percentage of stained cells by strength of staining. The results were statistically correlated with patients' survival outcome.
Results: 1-4 cases were excluded because of insufficient viable tumor. The remaining cases (≥68) showed variable positive staining for the selected markers. Significant staining (score ≥100) was identified in 86% of cases stained for Akt, 55% of cases stained for NF-Kappa B, 37% of cases stained for m-TOR and only 12% of cases stained for VEGF. BRAF showed negative or weak staining (score <100) in 97% of cases.
Decreased VEGF expression (score <100) was significantly associated with NED, i.e. better prognosis ($p<0.05$). No significant association was demonstrated between the expression of the remaining proteins and the prognosis.
Conclusions: The majority of EFT cases express mTOR, AKT, VEGF and NF-kappa B proteins and do not express BRAF. EFT tumors may be amenable to treatment that targets the expressed proteins. High Akt expression suggests potential universal response to Akt-targeted therapy. BRAF kinase inhibitors are unlikely to be effective in the treatment of Ewing's sarcoma family tumors. VEGF expression is related to prognosis and larger studies may be needed to correlate VEGF over-expression to patients' prognosis and document the effectiveness of VEGF inhibitors in the treatment of these patients.

19 microRNA Profiling in Adipocytic Neoplasms.

WA Ahrens, NM Steuerwald, JC Patt, JS Kneisl, HL Bonkovsky. Carolinas Medical Center, Charlotte, NC.
Background: MicroRNAs (miRNAs) are a class of small noncoding RNAs. They have been shown to promote or suppress tumorigenesis in human cancers by altering cancer-related gene expression. Subtype-specific expression patterns are emerging in various types of sarcoma. In this study, miRNA expression profiling was performed in 18 adipocytic tumors.
Design: Snap-frozen tumor was collected from 7 well-differentiated liposarcomas (WDLS), 4 myxoid liposarcomas (MLS), 2 lipoblastomas (LB) and 5 lipomas (LP). Non-neoplastic adipose was collected in 6 cases as control. RNA was isolated using Qiagen miRNeasy. RNA was Poly A tailed and ligated to biotinylated signal molecules using the FlashTag Biotin RNA labeling Kit (Genisphere). An Enzyme Linked Oligosorbent Assay QC assay was performed to verify labeling prior to hybridization to GeneChip miRNA Arrays (Affymetrix, Santa Clara, CA). Hybridization, washing, staining and scanning was performed using Affymetrix GeneChip system instruments. Affymetrix GeneChip Operating Software version 1.4 was used to analyze microarray image data and to compute intensity values. Partek Genomic Suite (Partek Inc., St. Louis, MI, USA) was used to compute fold changes and perform statistical analyses.
Results: Tumor subtype principal component analysis is shown in figure 1.