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PLATFORM and POSTER PRESENTATIONS

Autopsy

1 The Effect of Time Between Patient Death and Tissue Collection on RNA Integrity of Metastatic Tumors

Tarek Abi-Saab, Prashant Bavi, Julia Jiang, Madura Siva, Dianne Chadwick, Anthony Joshua, Michael Roehrl. University Health Network, Toronto, ON, Canada.

Background: The Rapid Research Autopsy Program at the Princess Margaret Cancer Centre was created to allow the rapid banking of metastatic tumors from end-of-life patients to enhance our understanding of tumor development. Research tissue sampling is done on consented patients as soon as possible after death, but may be delayed for 24 hours or more. The purpose of this study was to determine the effect of time between patient death and tissue processing on RNA integrity.

Design: RNA integrity number (RIN) scores were determined for primary tumors, metastatic lesions and normal uninvolved tissues from patients consenting to the Tissue Procurement Program. The time between patient death and tissue processing was recorded. RIN scores were determined on snap frozen tissue using a bioanalyzer (Agilent) and reported on a scale of 1-10, with 10 indicating fully intact RNA, 5 indicating partially degraded RNA, and 3 indicating fully degraded RNA.

Results: RIN scores of the primary tumor, a liver metastasis and normal kidney from a patient with lung cancer sampled 5 hours post mortem were 5.6, 7.6 and 4.8 respectively. Tumor tissues collected from a second patient with lung cancer sampled 18 hours postmortem had RIN scores of 6.6 (primary) and 6.9 (liver metastasis). Normal kidney had a reading of N/A (completely degraded). RNA quality differed between tissue sites in one patient with pancreatic cancer, with RIN scores that ranged from 8.6 (peritoneum metastasis) to N/A (hepatic lymph node metastasis). A RIN analysis has since become routine QC for all patients in our rapid autopsy program (3-5 new patients per week).

Conclusions: The results of this study indicate that RNA integrity of metastatic tumors can be maintained more than 18 hours after death, whereas normal tissues may be more sensitive to RNA degradation post mortem. Results also indicate that some tissue sites within the body preserve RNA quality better than others. Analysis of RNA from metastatic lesions of patients participating in the Tissue Procurement Program may provide valuable insights into tumor evolution and resistance to treatment.

2 Standardized Autopsy Report and Online Death Certificate in Portugal – A Joint Collaboration of the College of Pathology and the Directorate-General of Health (DGS)

Antonio Alves, Pedro Luis, Pedro Oliveira, Marco Ferreira, Catia Sousa Pinto. Centro Hospitalar Lisboa Norte, Lisbon, Portugal; Hospital da Luz, Lisbon, Portugal; Ordem dos Medicos, Lisbon, Portugal; Hospital CUF Descobertas, Lisbon, Portugal; Direcao Geral de Saude, Lisbon, Portugal.

Background: January 2014 was a hallmark in autopsy registry in Portugal. A national electronic online-only death certificate platform was established. This led to the creation and implementation of a national standardized protocol, which could be used internationally, for reporting the clinical autopsy. In October 2014, this protocol was integrated in the electronic platform.

Design: A national core panel of pathology residents, under the supervision of the Portuguese College of Pathologists, gathered to develop a reference database for adult clinical autopsy reporting. This online platform was aimed to be a user-friendly scheme, easy to fill, structured as a conventional autopsy report and divided by organ systems; it is pre-loaded with a minimal "normal" default data and a selectable pathology field, loaded with the most common pathological findings; however it always offers a free-text option, whenever necessary or as an alternative. In the end, the data is submitted to the death certificate registry and a pdf file can be created with the full clinical autopsy report.

Results: This revolutionary new resource, now implemented, similar to cancer protocols, is intend to not only stimulate the correct and complete recording of all autopsy findings (in an easy way), but also to allow the creation of a national database, that is going to be a promising new tool for medical research on major causes of death, most frequent organ pathologies, and possibly with improvement of detection and prevention of diseases.

Conclusions: It is anticipated that this new platform, more than just standardizing the autopsy report, can be used by other countries, and in a near future allow the creation of a worldwide database, contributing for the revival of autopsy as a medical tool, as a quality assessment procedure in medical practice, possibly reverting the decline in autopsy rates and stimulating the importance of autopsy in the daily practice of pathologists.

3 A Cancer Center's Large-Scale Rapid (Warm) Autopsy Program: Unique Insights Into Tumor Kinetics and Biology

Prashant Bavi, Madura Siva, Jagdish Butany, Anthony Joshua, Michael Roehrl. University Health Network, Toronto, ON, Canada.

Background: Autopsy rates are globally on the decline. This is especially true for terminal cancer patients where autopsies are very rarely performed. Our comprehensive program was started to provide a fast and reliable way to harvest high-quality spatially indexed biospecimens for cancer research that represent disease biology, intrinsic heterogeneity (primary, metastases, etc.) and spatially differential treatment response (e.g., tyrosine kinase inhibitor resistant vs. sensitive lesions, irradiated vs. native) within the same patient.

Design: So far, 37 patients who had consented to undergo rapid autopsies have been enrolled and studied. Our current rate of accrual is 3-5 patients per week. We focus on the following aspects: (1) Tumor kinetics by integrating radiographic imaging findings and tumor burden; (2) metastasis to distant organs and unusual sites; (3) presentation and metastatic spread of rare and unusual neoplasms; (4) integrated collection of tissues and body fluids. Samples from our program will typically be studied by deep genome sequencing, transcriptomics, and proteomics. Furthermore, many samples are used for patient-derived xenografting and ex vivo organoid cultures of tumors.

Results: In our series of 37 autopsies, patient age ranged from 24 to 86 years (median, 66 years), 18 males and 19 females, cancer types were 6 lung cancers, 4 melanomas, 4 pancreatic carcinomas, 3 hematological malignancies, 3 colorectal cancers, 3 prostate cancers, 2 breast cancers, 2 bladder cancer, 2 sarcomas, 2 gastric cancers, 1 cholangiocarcinoma, 1 endometrial cancer, 1 ovarian, 1 renal, 1 salivary gland, and 1 pelvic squamous cell carcinoma. There was significant underestimation of tumor burden at last imaging in virtually all patients. The heart was involved in 3 cases: 2 melanomas and 1 pancreatic cancer. Patient-derived xenografts and ex vivo organoids were successfully grown from numerous lesions. Whole genome sequencing, RNA-Seq, and proteomics experiments using mass spectrometry have also been carried out successfully.

Conclusions: Mechanisms of treatment escape of cancers remains a fundamentally unadressed issue in cancer research and clinical trials. Rapid research autopsies are a powerful tool for cancer research. Our program allows the otherwise impossible comprehensive deep molecular analysis of events that contribute to cancer metastasis, spatiotemporal heterogeneity, differential treatment response, and ultimate treatment escape of lesions under targeted therapies.

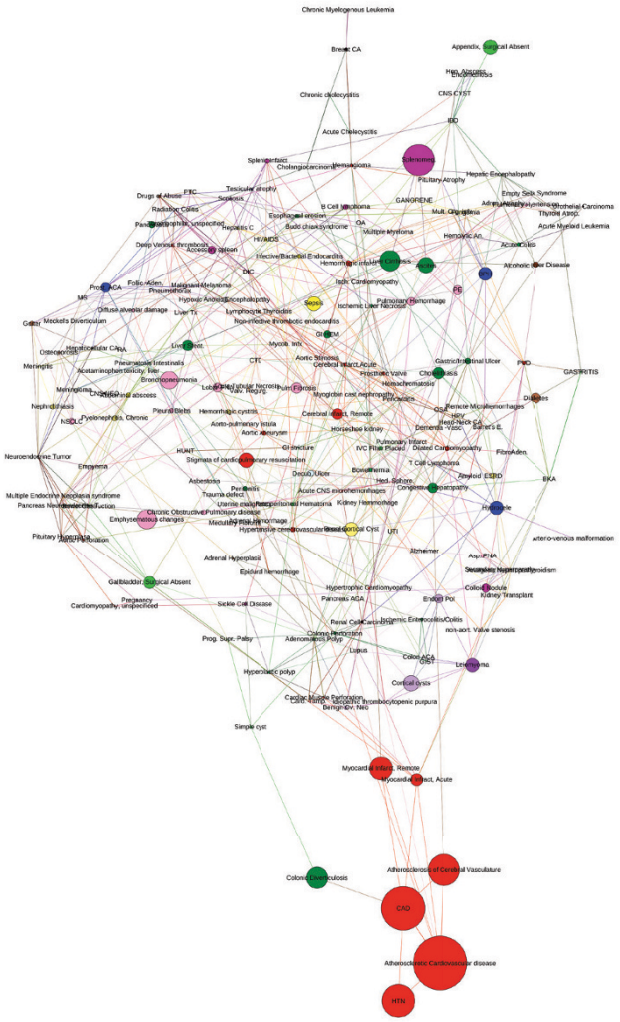
4 The Pathomorbidome: A System Network Analysis of Comorbidities Documented at Autopsy

Romulo Celli, Miguel Divo, Monica Colunga, Kisha Mitchell. Yale University New Haven Hospital, New Haven, CT; Brigham & Women's Hospital, Boston, MA; Sciences Po, Paris, France.

Background: Autopsies provide anatomic evidence of diseases, and autopsy reports are a reliable tool for assessing disease prevalence. To our knowledge, no study to date has investigated the relationships between numerous diseases documented simultaneously in one population. In this study, we describe an autopsy comorbidity network by exploring co-occurrence clusters using network graphic analysis.

Design: Autopsy reports of all patients who underwent full autopsy at Yale-New Haven Hospital in one academic year period (2012-2013) were retrospectively reviewed. Comorbidities were recorded systematically. Spearman's coefficient were calculated between comorbidities, and those with significant correlation ($p<0.001$) were selected to construct the network. Each comorbidity is represented by a node, and the size of the nodes represent their prevalence. The edges represent paired correlations, and the thickness of the edge is proportional to ρ (rho). We calculated the relation among connections and prevalence, and also explored clusters of correlated diseases.

Results: The study group consisted of 136 patients (56% men) with a mean age of 61 years. The mean BMI was 30 kg/m^2. There were 199 diseases/conditions, each represented by a node and providing 662 significant correlations (equal to the number of edges in the graph, Figure 1). The mean degree (number of connections per node) was 7. Ten motifs, or clusters of highly associated diseases, were identified. Some motifs exhibit stereotyped associations which are highly prevalent in medicine, such as atherosclerotic cardiovascular disease with hypertension and myocardial infarct. Others show less obvious correlations; for example, between papillary thyroid carcinoma, drug abuse, and thrombophilia.



Conclusions: We introduce a new method of autopsy data analysis. In this network particular motifs are identified which represent the building blocks of the network graph. These motifs represent patterns of disease which may be expected to occur together at the time of death and may be amenable to further interventions during life.

5 Clinical History, Cause of Death, Laboratory and Autopsy Findings of Patients With Undiagnosed Hematological Malignancy: A Retrospective Study

Jennifer Dierksen, Maximilian Buja, Lei Chen. University of Texas, Houston, TX.

Background: Hematological malignancies can exhibit many clinical presentations, ranging from ambiguous systemic symptoms to rapid onset of multi-organ failure. These nonspecific symptoms may hinder the timely diagnosis of a hematological malignancy and increase mortality. By identifying common clinical, laboratory, and autopsy findings in patients who died from a hematological malignancy, living patients may be diagnosed earlier and receive life-saving treatment.

Design: We retrospectively reviewed our institution's 2003-2013 autopsy and respective medical records for patients with a hematological malignancy. Patient history, autopsy findings, and laboratory data were recorded.

Results: 30 autopsy patients were identified, including 13 "acute" cases diagnosed at (6 cases) or within 1 month of autopsy. Acute patients most frequently presented with pain, dyspnea and gastrointestinal symptoms. Acute lymphoma patients survived 9.4 days and had symptoms for 22.3 days; acute leukemia patients had 4.3 and 16 days, respectively. Common initial laboratory findings for acute lymphoma patients included elevated LDH, (9/10), AST (8/10) and prothrombin time (PT) (7/8), lactic acidosis (5/5), progressing anemia (7/8) and platelet decline. Acute leukemia patients had peripheral smear findings, thrombocytopenia (3/3), normal liver enzymes (2/3), elevated PT (3/3), lactic acidosis (2/2) and elevated LDH (2/2). Patients with an established diagnosis had similar findings with increased thrombocytopenia in lymphoma cases. Common autopsy findings include large pleural effusions, pulmonary congestion, ATN, and bone marrow involvement. Hepatomegaly occurred in all patients with leukemia or infiltrating lymphoma, but not in patients with mediastinal or gastrointestinal lymphoma. Splenomegaly occurred in all leukemia cases but less frequently and severely in lymphoma cases. 4/6 acute patients had a diagnostic pre-mortem tissue biopsy. Immediate causes of death were cardiopulmonary arrest and multi-organ failure through malignant infiltration of organs and/or septic shock due to the immuno-compromised state.

Conclusions: Lactic acidosis, elevated LDH and PT, bone marrow involvement and hepatomegaly in our study are pertinent findings of an acute infiltrating lymphoma or leukemia. From these results, we aim to increase consideration of a hematological malignancy in a critically ill patient after initial laboratory and clinical findings, leading to an earlier diagnosis by tissue biopsy and subsequent treatment.

6 Prevalence of Papillary Thyroid Microcarcinoma in Mexico – An Autopsy Study

Armando Gamboa-Dominguez, Fernando Cano-Garcia, Mariana Tenorio-Serralta. National Institute of Medical Sciences and Nutrition, Mexico City, Tlalpan, Mexico.

Background: Geographical variations in the prevalence of papillary thyroid microcarcinoma (PTM) have been reported in postmortem series ranging from more than 50% to 2%, but no information is known from Mexican population. Objective: identify the prevalence of PTM and its demographc characteristics in a large autopsy series.

Design: In a teaching hospital, a prospective autopsy study of formalin preserved glands sectioned at 2-4mm wide and independently reviewed was performed. Clinical, demographic, gross and microscopic characteristics of the glands and tumors were recorded. Thyroids were almost completely submitted for histologic review. The presence of concomitant thyroidal diseases was described as well as a descriptive analysis of the findings.

Results: Three hundred sixthy seven autopsies were performed with an extensive analysis of the thyroid gland and 29 (prevalence 7.9%) papillary microcarcinomas were found. Gland weight range from 8-28g and were grossly normal in patients from 16 to 88 year old. The smallest tumor was 0.05mm and the larger 7mm, in six thyroids more than one lesion was observed (multifocality 1.6%). A 1:1 male/female ratio was observed and most of the tumors were observed in person from 35 to 60 years. A follicular pattern of growth was observed in 18/29 tumors (62%) with minimal fibrosis. Multinodular goiter was the most frequent associated disease and only one gland showed Hashimoto´s thyroiditis that correlated with anti-thyroid antibodies.

Conclusions: The observed prevalence of papillary microcarcinoma of the thyroid is similar to that of Brazilian population and below to that of Finland, Japan or USA. A constant in all published autopsy series is the similar prevalence among genders, suggesting that hormonal influences in thyroid carcinogenesis could explain the high prevalence of this tumor in clinically detected lesions. No association was observed of papillary microcarcinoma with chronic thyroiditis.

7 A Tell-Tale Heart of Fabry Disease

Andrew Guajardo, Mingjuan Zhang, Marc Halushka, Barbara Crain. Johns Hopkins Hospital, Baltimore, MD.

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease affecting approximately 1 in 100,000 live births. Deficiency of the enzyme alpha-galactosidase A leads to accumulation of globotriaosylceramide, causing multi-system dysfunction affecting the kidneys, heart, central and peripheral nervous systems, skin, eyes, gastrointestinal tract, and less commonly, the lung. Homozygous males typically present with severe disease by the second decade; however, heterozygote female symptomology varies widely, resulting in initial misdiagnosis. Since accumulation of glycosphingolipids likely increases with time, early diagnosis and prompt enzyme replacement therapy are essential to mitigating the dysfunctional effects.

Design: We present an autopsy of a 64-year-old female who was treated for nonspecific interstitial lung disease for ten years. She also presented with peripheral parasthesias as well as mildly elevated creatinine. After multiple upper respiratory infections, she no longer responded to therapy. Subsequent examination of the heart revealed left ventricular hypertrophy with features suggestive of infiltrative myopathy initially believed to be amyloidosis or a rheumatologic disorder. However, a heart biopsy unexpectedly showed the presence of myelin figures. This prompted testing for levels of alpha-galactosidase A, which were in the low normal range, and a genetic mutational analysis, which showed a heterozygous mutation in GLA p. Gln279Glu(c. 835C>G) confirming FD.

Results: Autopsy findings included extensive accumulation of storage products predominantly within the myocardium. Examination of the electrical conduction system found involvement of the atrioventricular node. The renal system did not show the typical renal sinus cysts, and light microscopy showed no vacuolization; however, electron microscopy was significant for myelin figures within the glomerular podocytes. The lungs were markedly involved by a non-specific interstitial fibrosis and pulmonary emboli of various ages. The final cause of death was infiltrative cardiomyopathy due to FD.

Conclusions: The clinical course and autopsy demonstrate the difficulty and importance of considering FD when presented with abnormalities in multiple organ systems. While cardiac manifestations typically accompany other findings of FD, they can occasionally occur as the sole manifestation in patients with the "cardiac variant", which appears to have been the case in this patient. A high index of suspicion and early diagnosis would allow patients to benefit from treatment prior to the extensive accumulation of glycosphingolipids.

8 Retinocochleocerebral Vasculopathy (Susac Syndrome): First Report of Autopsy Examination

Nicholas Harding-Jackson, Elizabeth Cochran. Medical College of Wisconsin, Milwaukee, WI.

Background: Susac Syndrome (SS) is a rare disorder characterized by a clinical triad of visual loss due to retinal artery occlusion, hearing loss, and acute/subacute multifocal neurologic symptoms, or any combination of these. The etiologic basis is unknown, but it is hypothesized to be an autoimmune microangiopathy, and anti-endothelial cell antibodies have been identified in a subset of reported cases. Diagnosis is usually based

on clinical presentation, audiometry, fluorescein angiography and brain MRI. To date, although retinal tissue and muscle, skin, and brain biopsy findings have been reported, this is the first autopsy report of SS.

Design: We report a case of a 59 year old woman with a clinical diagnosis of SS, based upon sensorineural hearing loss and multiple brain infarcts who presented with sepsis secondary to a urinary tract infection. In the three years prior to her death, she was hospitalized three times due to acute onset of focal neurologic symptoms, and treated with immunosuppression. She also had a history of interstitial lung disease, squamous cell carcinoma of lung, colon carcinoma, hypertension, and cataracts. An unrestricted autopsy was performed. Formalin-fixed and paraffin-embedded tissue samples were processed for histologic and immunohistologic (IHC) examination.

Results: Extensive degeneration of the corpus callosum is present, with macroscopic and microscopic infarcts which also involve the cortex, centrum ovale, and thalamus. Luxol fast blue stain and neurofilament IHC show myelin and axonal loss, respectively. Small arterioles show adventitial thickening, positive for collagen IV IHC, and negative for amyloid with Congo-Red stain and β-amyloid IHC. Sparse CD3 immunoreactive perivascular and parenchymal lymphocytes are present without vasculitis, fibrinoid necrosis, fibrin thrombi, or significant endothelial cell loss. Additional autopsy findings include: fibrotic non-specific interstitial pneumonitis and secondary pulmonary hypertensive changes.

Conclusions: Prior reports of brain biopsies in acute exacerbations of SS have emphasized endothelial cell damage and fibrin thrombi. We extend the morphologic and immunohistochemical characterization of this entity through report of an autopsy case of chronic SS with collagenous thickening of small arterioles, intact endothelial cells, sparse inflammatory infiltrates, predominantly white matter infarcts severely affecting the corpus callosum, and uniquely associated with non-specific interstitial pneumonitis.

9 Acute Thymic Involution in Third Trimester Stillbirth: Frequency, Grade, and Correlation With Neuropathological Injury

Suzanne Jacques, Seema Sethi, William Kupsky, Faisal Qureshi. Hutzel Women's Hospital/Wayne State University, Detroit, MI.

Background: Despite detailed autopsy examination, many 3rd trimester stillbirths (SB) remain unexplained, including the nature and timing of onset of illness. We frequently find acute thymic involution (ATI) in 3rd trimester SB. ATI in infancy, when graded on a 5 point scale, correlates with the duration of acute illness (grade 0 <12 hrs; grade 4 >72 hrs). Antenatal hypoxic/ischemic gray matter injury (GMI) and white matter injury (WMI) are also frequent findings in SB, with histologic neuronal necrosis likely requiring >48 hrs to develop. This autopsy series is the first to investigate frequency and grade of ATI in unexplained SB, and correlate it with brain injury.

Design: We identified autopsies of 3rd trimester unexplained SB, all with brain examination by a neuropathologist. Histologic ATI was graded from 0 (resting state) to 4 (pronounced lymphodepletion) based on appearance of macrophages, increase in interstitium, and lymphodepletion of cortex. For analysis, ATI grade 0-1 and 3-4 were combined. GMI was classified as older (neuronal necrosis with karyorrhexis) or recent (red neurons without older GMI), and WMI was classified as older (periventricular leukomalacia with necrosis or gliosis) or recent (reactive glial changes or edema without older WMI). ATI was also correlated with thymic wt and clinical data.

Results: We identified 58 SB autopsies; 49 (84%) had grade 2-4 ATI (table). 34 were preterm and 24 term; 17 (50%) preterm SB had grade 3-4 ATI, compared to 13 (54%) term (p=NS). ATI correlated significantly with the presence and age of GMI (p<0.001) and WMI (p=0.032) (table). Lower thymic wt showed a trend toward higher ATI grade (p=NS). Of clinical features evaluated, including diabetes and hypertension, grade 3-4 ATI correlated only with small for gestational age (12/15; 80%) vs normal/large for gestational age SB (18/43;42%) (p=0.001).

ATI grade (# of cases)	Thymic wt (g)	Older GMI	Recent GMI	No GMI	Older WMI	Recent WMI	No WMI
0-1 (n=9) (16%)	6.3+/-3.3	1 (3%)	2 (25%)	6 (55%)	0	3 (20%)	6 (18%)
2 (n=19) (33%)	6.3+/-3.1	10 (26%)	5 (63%)	4 (36%)	1 (10%)	5 (33%)	13 (39%)
3-4 (n=30) (52%)	4.9+/-3.7	28 (72%)	1 (13%)	1 (9%)	9 (90%)	7 (47%)	14 (42%)

Conclusions: Grade 2-4 ATI was found in a majority (84%) of unexplained 3rd trimester SB c/w onset of acute illness 24->72 hrs before demise. ATI grade correlated significantly with presence and age of GMI/WMI, suggesting similar time of onset and shared underlying pathophysiologic events, the specific nature of which remains unclear.

10 Clinicopathologic Findings in Acute Esophageal Necrosis (AEN)-Related Mortality

Hope Karnes, Kirk Hill, Horacio Maluf. Washington University School of Medicine, St. Louis, MO.

Background: Acute esophageal necrosis (AEN) or black esophagus is a rare pathologic entity associated with 30% mortality. AEN is defined by circumferential esophageal necrosis, which ends abruptly at the Z-line. Macroscopically, the affected area is strikingly black. AEN has been clinically linked to gastric outlet obstruction, ischemic injury, and hemodynamic instability, but the pathophysiologic mechanism remains largely unknown. AEN frequently causes death; however, there is a dearth of cases reported in the autopsy literature. The objective of this study is to correlate clinical and postmortem findings of AEN.

Design: A 20-year retrospective review of our autopsy database was conducted using the following search terms: "black esophagus" and "necrosis AND esophagus." Histologic sections and final autopsy reports were reviewed to assess the severity of esophageal necrosis and determine the contribution to death. Medical records were also reviewed for demographic information, endoscopic findings, and medical comorbidities.

Results: Fourteen cases of esophageal necrosis were identified. In 9 (64.3%) cases, esophageal pathologies were secondary findings, not contributing to the cause of death. In one (7.1%) case, focal esophageal mucosal ulceration with fibrinopurulent debris and necrosis was considered contributory to sepsis. AEN was implicated in the immediate cause of death in three (21.4%) cases, and one additional case of AEN, with gross discoloration of the esophageal mucosa but an indeterminate cause of death reported, was identified retrospectively during this study. In all cases of AEN-related mortality, the decedents were men. The average age (68.3 years) of individuals dying from AEN was higher than for individuals with isolated esophageal pathologies (25.9 years), and the latter group consisted of more women (70%) than men. In our series, death from AEN was associated with male gender, advanced age, gastrointestinal (GI) bleeding, malignancy, cirrhosis, hepatitis C infection, smoking, and vascular disease. Two AEN cases had antemortem endoscopic evidence of black mucosal discoloration, and one showed only blood. Histologically, esophageal necrosis was diffuse in AEN, with only focal, superficial necrosis seen in non-AEN cases.

Conclusions: AEN-related mortality in our series was 28.6% and occurred most frequently in older men with GI bleeding. Histologically, diffuse esophageal necrosis was noted in AEN cases. AEN represents a rare but important cause of death, of which pathologists should be aware.

11 POEMS Syndrome: A Study of Five Autopsy Cases With Emphasis on the Significance of Subcutaneous Calciphylaxis

Asuka Kawano, Satoshi Ota, Takashi Oide, Jun Matsushima, Masaki Suzuki, Masami Iwamoto, Takashi Kishimoto, Motoo Kitagawa, Nobuyuki Araki, Sonoko Misawa, Satoshi Kuwabara, Emiko Sakaida, Chiaki Nakaseko. Chiba University School of Medicine, Chiba, Japan.

Background: POEMS syndrome (POEMS) is a multisystemic disorder characterized by polyneuropathy, organomegaly, endocrinopathy, presence of M protein, and skin changes. Calciphylaxis is a rare life-threatening condition that is characterized by calcification of small- to medium-sized blood vessels leading to progressive cutaneous necrosis, usually seen in patients with chronic renal failure and secondary hyperparathyroidism. Although there have been few reports of calciphylaxis in POEMS, its detailed pathology and clinical significance are not clear.

Design: Among 83 cases diagnosed as POEMS syndrome from 1993 to 2014 in Chiba University, there were 19 fatal cases and 5 of them underwent autopsy. Histopathological study of the 5 autopsy cases was performed together with the analysis of biopsy specimens and clinical information including the evaluation of subcutaneous calcification of the femoral area in 76 cases by CT scan.

Results: Calciphylaxis were observed in 3 autopsy cases and 1 biopsy case. Microscopically, intimal proliferation and thickening of the wall of blood vessels with marked medial calcification were commonly observed in the subcutis and other sites. Clinically, CT scan analysis revealed femoral subcutaneous calcification, suggesting the possibility of calciphylaxis, in 16% (12/76). All 5 autopsy cases showed markedly elevated serum VEGF levels. Osseous sclerotic lesions with moderate fibrosis were present in 2 cases, and a clonal plasma cell proliferation of IgGλ type in bone marrow was immunohistochemically confirmed in 1 case.

Conclusions: Histopathological findings observed in 3 autopsy cases suggest that calciphylaxis is an under-recognized characteristic condition of POEMS. The unique findings of calciphylaxis in POEMS call for further investigation in the underlying pathogenesis and molecular mechanism, especially with reference to high serum VEGF levels and clonal plasma cell proliferation.

12 Pulmonary Vascular-Proven Causes of Death in Lungs of Patients With Sudden Unexpected Death in Patients not on Antihypertensive Therapy. Emphasis on Congenital Heart Disease, Eisenmenger Syndrome, Post Operative Deaths and Death During Pregnancy and Post Partum

Dimitra Krexi, Mary Sheppard. Aristotle University of Thessaloniki, Thessaloniki, Greece; St. George's Hospital Medical School, London, United Kingdom.

Background: Pulmonary hypertension in asymptomatic patients is a rare cause of sudden death. This study aims to determine the incidence of this entity and raise awareness amongst pathologists.

Design: We retrospectively investigated 44 cases of sudden unexpected death in relation to pulmonary hypertension in patients not on antihypertensive therapy. This is the largest pathological study reported.

Results: We report 44 cases of sudden death due to pulmonary hypertension in which 28 (63.63%) were female and 16 (36.36%) were male and the age range was from 5 days to 93 years old (mean age: 24±20). All had been well prior to death with none on therapy for pulmonary hypertension. The majority died at rest, 18 cases (40.90%) while 7 patients (15.90%) died following cardiac surgery and 7 patients (15.90%) during pregnancy or post-partum, 6 of whom had congenital heart disease. The cause of pulmonary hypertension was recognised as congenital heart disease in 27 patients (61.36%), 14 of whom had simple congenital heart disease such as atrial or ventricular septal defect and 13 had complex congenital heart disease with associated ASD or VSD. The remaining 17 patients (29.55%) suffered from primary pulmonary hypertension due to plexiform arteriopathy, veno-occlusive disease, and thromboembolic disease. Extensive sampling of the lungs is required to detect the lesions microscopically in these conditions.

Conclusions: It is important that pathologists be aware of the risk of sudden unexpected death in asymptomatic patients with pulmonary hypertension, especially in those with congenital heart disease, after cardiac surgery or pregnancy.

13 Congenital Lymphangiomatosis: A Histologic and Immunohistochemical Study of Four Fetal Autopsies

Jiancong Liang, Qiang Xie, Virginia Anderson. SUNY Downstate Medical Center, Brooklyn, NY.

Background: Lymphangiomatosis is an under-recognized developmental malformation that often presents with diffuse involvement of parenchymal organs, bone, skin and soft tissue. Although lymphangiomatosis can present at birth, studies on its occurrence in developing fetuses are lacking. To our knowledge, this is the first study on lymphangiomatosis in fetuses.

Design: We describe four fetal autopsies of lymphangiomatosis with predominant involvement of two or more organs and/or soft tissue. The gestational age was 19, 22, 24, and 31 weeks.

Results: Three of the four fetuses were female. Three cases showed intrauterine growth retardation. Marked accumulation of pericardial, plural and peritoneal fluid was seen in one case. The often involved anatomic sites included the skin (2 cases) and gastrointestinal tract (2 cases). Involvement of the tracheal mucosa, peri-adrenal soft tissue, diaphragm and renal pelvis was also seen. Histologic examination showed dilated, anastomosing thin-walled channels that contain lymphatic valves and are lined by flat endothelial cells. Immunohistochemical studies with D2-40 and CD31 antibodies showed that all cases were positive for at least one of these two markers for lymphatic endothelial cells. In our experience, the combination of two markers is useful in highlighting the lymphatic channels and confirming the diagnosis. This appears to be particularly contributory when significant tissue autolysis is encountered due to intrauterine fetal demise and delayed delivery. Chromosomal analysis was performed in one case and demonstrated trisomy 21.

Conclusions: Congenital lymphangiomatosis involves multiple organs and may contribute to the process leading to intrauterine fetal demise. When used together, immunohistochemical stains for D2-40 and CD31 highlight all lesions. Genetic aberrations may be a significant etiologic factor for congenital lymphangiomatosis in stillborn fetuses.

14 Post-Mortem Analysis of Methylene Blue Distribution Following Its Use as Treatment for Refractory Shock

Lindsey Lowder, Wujuan Zhang, Divya Sharma, Melita Skelton, Rita Angel, Kenneth Setchell, Roger Smith. University of Cincinnati Medical Center, Cincinnati, OH; Cincinnati Children's Hospital and Medical Center, Cincinnati, OH.

Background: Methylene Blue (MB), a versatile synthetic drug used over 100 years as an anti-malarial agent, a staining reagent, and a treatment for methemoglobinemia, has had many applications in the fields of medicine and chemistry. It's potential utility in treating refractory shock is being explored and studies suggest that MB inhibits guanylyl cyclase, preventing vasodilation. An analysis of MB's metabolite distribution in the setting of systemic shock is limited.

Design: We report a case of a 44 year-old female history of intravenous drug use, treated emergently with several parenteral infusions of MB for refractory septic shock. Ultimately, she expired and a full autopsy was completed. Mass spectrometric analysis of the liver, blood, vitreous and brain was done on Waters Xevo G2-S Q-TOF accurate mass spectrometer. The samples were added to methanol, vortexed and centrifuged to remove proteins. The liver was homogenized and extracted by a similar protein precipitation procedure with methanol. The supernatant of both the biofluid and tissue extracts were diluted with acetonitrile/water and charged with formic acid for mass spectrometric analysis. Q-TOF acquisition was done under positive scanning mode and scanned with a mass range of 50-1200 Da with direct infusion of samples.

Results: At autopsy, the heart and brain noticeably became green tinged, which intensified the longer they were exposed to ambient air. After formalin fixation, the color change ceased in progression. Histologic examination showed complications of severe sepsis. MB was found in all autopsy specimens with protonated ion showing an accurate mass m/z of 284.1324 and confirmed with existence of fragments at m/z of 268.0997 and 240.0773. The MB metabolite, Azure B was also found in blood, vitreous and liver tissue with protonated ion showing up at m/z 270.1170 and characteristic fragments at m/z 254.0860 and 228.0822.

Conclusions: This case presents novel insight into the MB metabolite distribution characteristics when used as treatment for refractory shock. Quantitatively, the MB level in the blood was 10 times higher than it was in the vitreous and was about the same level as in liver. It's metabolite, Azure B was found in all tissues examined. The distribution characteristics of methylene blue's metabolites aid in determining it's potential therapeutic benefit as an adjunct agent for refractory shock.

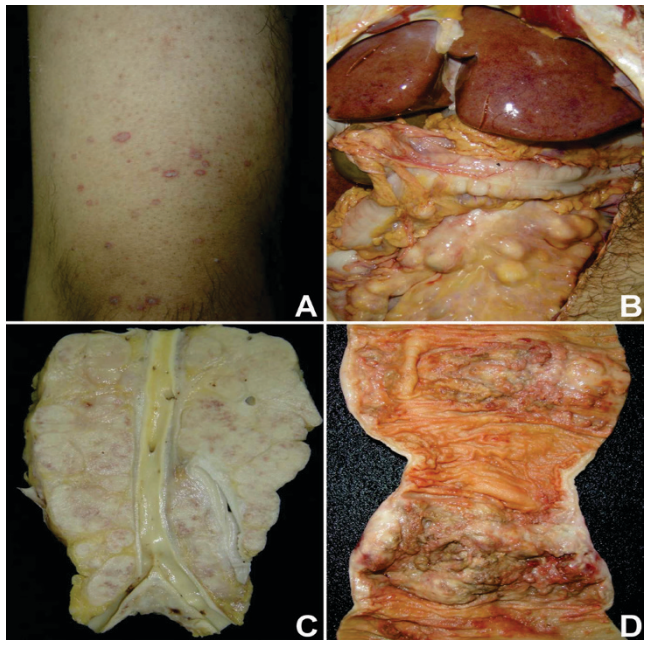
15 Disseminated Histoplasmosis in HIV/AIDS Patients Based on Analysis of Autopsy Cases

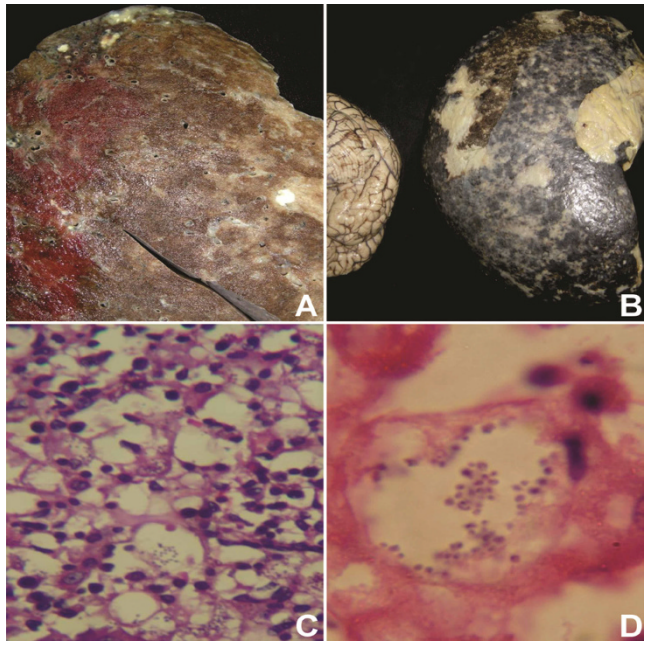
Julio Mantilla-Hernandez, Mario Melo-Uribe, Juan Idarraga. Universidad Industrial de Santander, Bucaramanga, Colombia; Universidad de La Sabana, Chia, Colombia.

Background: Histoplasmosis is a relatively common endemic mycosis in Colombia. Its disseminated form, occurs mostly in immunosuppressed patients, more frequently in patients with acquired immunodeficiency syndrome (AIDS) and CD4+ counts <50 cells/μL. This infection worsens these patient's clinical course even causing death.

Design: Autopsy records from the Pathology Department at Universidad Industrial de Santander, Colombia, between January 2004 and August 2014, corresponding to patients diagnosed with HIV/AIDS and disseminated histoplasmosis (DH) were analyzed. A rigorous morphological exam was performed and the descriptions and demographic variables were recorded in a database.

Results: Between the years 2004 and 2014, 2603 autopsies were performed. Out of these autopsies, 206 corresponded to HIV/AIDS patients, and 37 of these patients had DH (27 males and 10 females), with a mean age of 36,3 years and non-adherence to highly active antiretroviral therapy (HAART). All of them had CD4+ counts less than <50 cells/μL. Eight of these cases had a clinical diagnosis of histoplasmosis prior to death. The most commonly compromised organs in DH were the lungs (23 cases), lymph nodes (22 cases), liver and spleen (15 cases), bone marrow (8 cases), gastrointestinal tract, adrenal glands (5 cases), and skin (3 cases). Concomitant infections were found with Pneumocystis (3 cases), Tuberculosis (2 cases), Cytomegalovirus (2 cases), and Cryptococcus (1 case).





Conclusions: In this study, histoplasmosis is the most frequent fungal opportunistic infection in patients with HIV/AIDS and its disseminated form was responsible for the majority of deaths. Lung, lymph nodes, liver and spleen were the most commonly compromised organs (14 cases). On the other hand, skin lesions are rarely common in cases of DH. Finally, a low suspected index of DH exists in Colombia; therefore DH in HIV/AIDS patients is a diagnosis not to be missed.

16 Applying the Irish National Quality Assurance Programme in Histopathology To Autopsies in St. Vincent's University Hospital, Dublin, Ireland

Aoife McCarthy, Thomas Crotty. St. Vincent's University Hospital, Dublin 4, Ireland.

Background: The Irish National Quality Assurance (QA) Programme in Histopathology, launched in 2009, is managed by the Royal College of Physicians of Ireland and is led by the Faculty of Pathology. It aims to provide a framework that enhances timely, accurate and complete diagnoses, reporting and service.

The QA Programme states that autopsy case review should include both Coroner and Non Coroner case types, and the following key performance indicators should be

measured and reviewed yearly: the percentage of cases with toxicology, with histology, and with specialist neuropathological examination; and the turnaround time (TAT) of the autopsy final report.
Our aim was to measure the QA Programme key performance indicators at our institution over a two year period and to compare the results between the two years.
Design: The autopsy database in our institution was used to identify all autopsies performed between 1st January 2012 and 31st December 2013.
The autopsy reports were reviewed and the relevant data was extracted.
The case type was recorded according to whether toxicology, histology, specialist neuropathological examination, or any combination of the three were performed.
The TAT for each autopsy was calculated, being defined as the length of time between the date of autopsy and the date the final report was authorized. Turnaround times according to case types were recorded.
Results were collated in Microsoft Excel.
Results: There were 128 autopsies (97.7% Coroner, 2.3% Non Coroner) in 2012 and 154 autopsies (98.1% Coroner, 1.9% Non Coroner) in 2013.
Histology, toxicology and specialist neuropathological examination were performed in 100%, 35.9% and 31.2%, respectively in 2012, and in 100%, 39.6% and 29.8%, respectively in 2013.
The TAT for cases with histology only, histology and specialist neuropathological examination, histology and toxicology, and histology, toxicology and specialist neuropathological examination was 57.8, 60.6, 91.6, and 129.4 days, respectively in 2012, and 57.4, 78.6, 123.7, and 106.2 days, respectively in 2013.
Conclusions: The Irish National Quality Assurance Programme in Histopathology outlines key quality monitors with associated indicators by which our laboratory can monitor our activities and evaluate our performance.
The QA Programme is an evolving process, and national QA benchmarks in autopsy must now be developed to maintain high standards of quality and to achieve the best possible outcome.

17 Reliability of Body Size Measurements Obtained at Autopsy: Impact on the Pathologic Assessment of the Heart

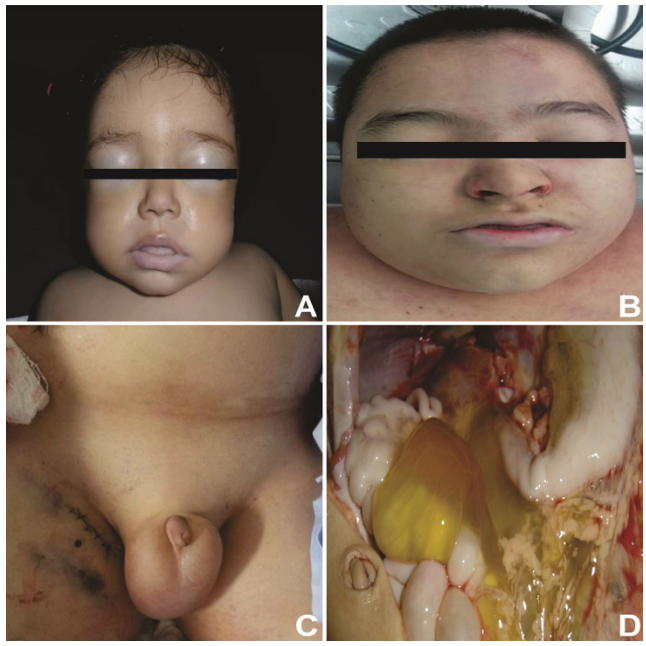
Carmen McCormack, Roberto Lo Gullo, Mannudeep Kalra, Abner Louissaint, James Stone. Massachusetts General Hospital, Boston, MA.

Background: Assessment of body size at autopsy is important for interpreting organ weight measurements and in some cases body identification. The objective of this study was to determine the reliability of post-mortem body size measurements, the causes for perturbations in these measurements from their corresponding pre-mortem values, and the impact of such perturbations on heart weight interpretation.
Design: Autopsy body length and weight measurements and pre-mortem height and body weight measurements were compared in 132 autopsies. Clinical records were evaluated for peripheral edema and serum albumin levels. Causes of death, body cavity fluid collections and heart weights were obtained from the autopsy reports. A subset of patients underwent quantitative post-mortem computed tomography (CT) assessment of anasarca.
Results: At autopsy, body weight differed from the pre-mortem value by 11±1%, compared with -0.2±0.3% for body length (P<0.0001). The percent change in body weight at autopsy correlated with the presence of peripheral edema (14±2% vs 7±2%, P=0.01), serum albumin <3.0 g/dL (16±2% vs 7±2%, P=0.001), and the degree of anasarca (P=0.01). In 4% of autopsies, heart weights were abnormal based on the pre-mortem body weight, but would be classified as normal based on the elevated post-mortem body weight.
Conclusions: At autopsy, body weight is a less reliable parameter than body length in correlating with the corresponding pre-mortem measurement. Autopsy body weights are elevated in part due to peripheral edema/anasarca. Alterations in body weight at autopsy can confound the interpretation of organ weight measurements.

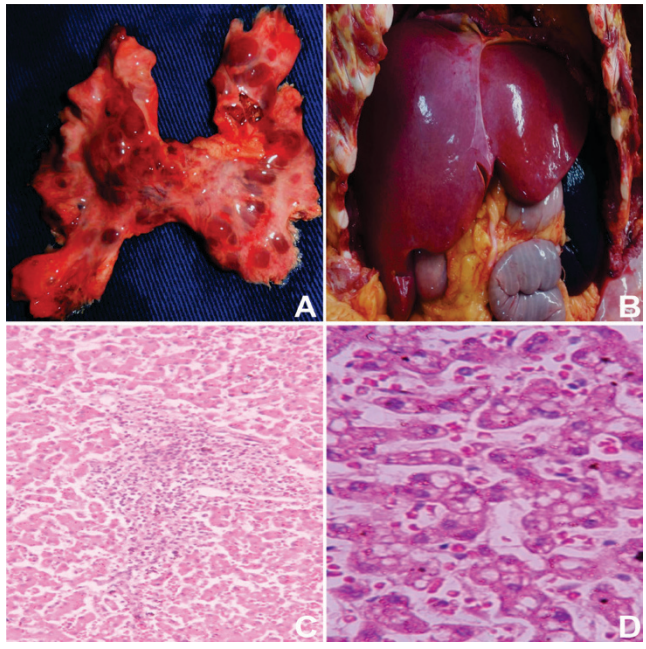
18 Deaths By Dengue Fever Base on Analysis of Autopsy Cases

Mario Melo-Uribe, Julio Mantilla-Hernandez, Juan Idarraga. Universidad de La Sabana, Chía, Colombia; Universidad Industrial de Santander, Bucaramanga, Colombia.

Background: Dengue is an arboviral disease transmitted to susceptible humans by the bite of an infected *Aedes aegypti* mosquito, and causes Acute Febrile Syndrome (AFS) with thrombocytopenia. Some infected patients may develop complications that may lead to death.
Design: Autopsy reports between January 2004 and August 2014, from a pathology department in Colombia were analyzed. Only those reports of patients in which AFS with thrombocytopenia was diagnosed, were gathered. Demographic and morphologic variables were analyzed.
Results: 2603 autopsies were performed, 110 corresponded to patients with AFS and thrombocytopenia, 70 males with a mean age of 30 years, ranging from 5 months to 93 years of age. Out of these 110 patients, 69,1% were actually dengue, 9,1% Staphylococcal sepsis, 4,5% bacterial meningitis, 3,6% bacterial endocarditis, and the rest corresponded to bacterial pneumonia, leptospirosis, yellow fever, acute Chagas disease, H1N1 pneumonia and pancreatitis. AFS with thrombocytopenia was diagnosed in 5 pregnant women who died. Dengue diagnosis was confirmed by IgM+ detection test (40 cases), RT-PCR (23 cases), IgM+ and RT-PCR (7 cases) and virus isolation (6 cases). The most frequent morphological findings in patients with dengue were soft tissue edemas, petechiae, jaundice, hepatomegaly, adenomegaly, hydrothorax, ascites, hydropericardium and splenomegaly.



Histological findings included lymphoid hyperplasia (95,7%), as well as pneumonitis (85,1%), hepatitis and Kupffer cell hyperplasia (80,8%), pericarditis (34%), myocarditis (17%), hepatocyte necrosis (12,7%), meningitis (10,6%), alveolar hemorrhage (4,2%) and other findings such as prominent endothelial cells, megakaryocytes in pulmonary capillaries, separation of myocardial fibers and alveolar edema.



Conclusions: In endemic areas, dengue is the most frequent cause of death in patients with AFS, even in pregnant women. The most common morphologic findings of dengue fever are described.

19 Postmortem Examination of Metastatic Carcinoma as the Cause of Death: A 10-Year Retrospective Review

Michaela Nguyen. New York Presbyterian Hospital – Weill Cornell Medical Center, New York, NY.

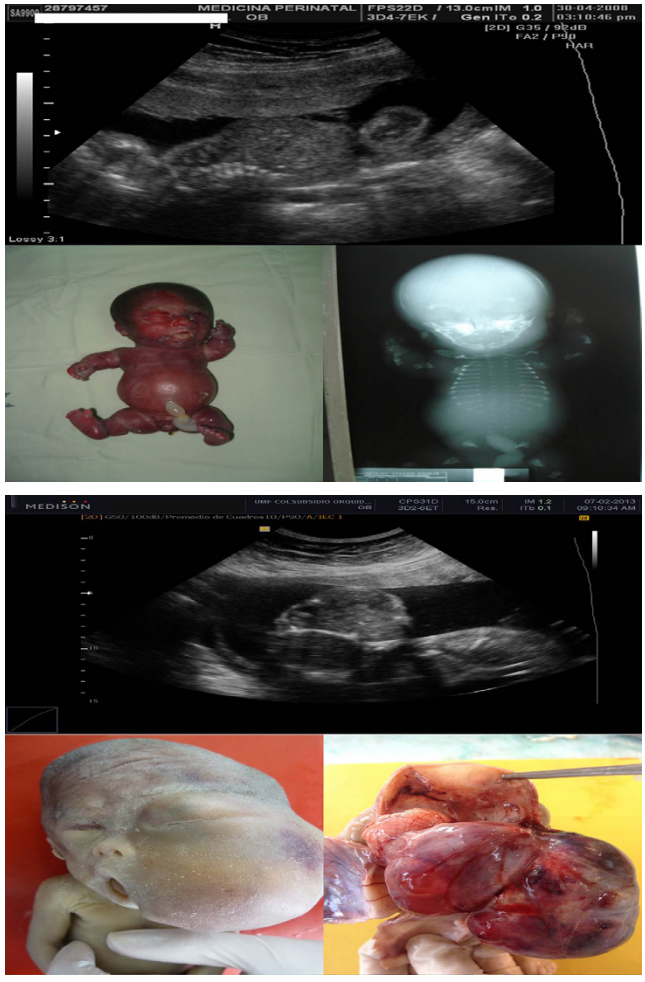
Background: Metastatic carcinoma of unknown origin (MUP) makes up 3% of all cancer deaths and poses a diagnostic challenge for clinicians and pathologists. Despite extensive diagnostic work-up, the primary origin was not identified in 70% of cases prior to death. The objective of this study was to characterize the value of postmortem examination in MUP at an academic institution over a 10-year period.
Design: We identified 199 patients with metastatic carcinoma as the cause of death, who had postmortem examination at our institution (1997 to 2007), in the institutional database. The electronic medical records and final autopsy reports were reviewed for each of the patient.
Results: Antemortem diagnostic work-up established the primary origin of the carcinoma in 152 of the 199 patients (76.4%). Carcinoma of lung origin was most frequently found (n=29, 19%), followed by breast (n=19, 12.5%), colon (n=18, 11.8%), pancreas (n=12, 7.9%), and upper gastrointestinal (n=13, 8.6%). Nine of the 152 patients

were diagnosed a different primary origin when compared with what was found at autopsy. Survival time after the initial diagnosis differed significantly between those with the concordant antemortem and postmortem diagnoses and those with discordant diagnoses (1304 days versus 135 days) ($p<0.05$).
Twenty-six of the 199 patients (13.1%) were clinically diagnosed with MUP prior to death. The top three most common primary found on autopsy was lung (n=7, 26.9%), followed by pancreas (n=4, 15.4%), and liver (n=2, 7.7%). The origin of the primary carcinoma could not be established in six of the 26 patients. The survival time after the initial diagnosis differed significantly between those where the primary origin was established and those where the origin could not be established (818 days vs. 369 days). Additionally, 21 of the 199 patients (10.5%) presented acutely without a diagnosis of carcinoma prior to death. Lung carcinoma was most frequently found (n=7, 30%). The origin of the primary carcinoma could not be established in 2 of the 21 patients. The immediate cause of death was related to complications of metastatic carcinoma.
Conclusions: Postmortem examination of patients with metastatic carcinoma, independent of origin, is necessary and valuable. Postmortem examination was able to establish the primary origin in 83% of patients with MUP. Despite treatments, patients in whom a primary origin could not be established during the antemortem period have a shorter survival time.

20 Pathological Correlation in the Cytogenetic and Ultrasound Prenatal Diagnosis – Based on Analysis of Autopsy Cases

Claudia Ortega, Carolina Mantilla, Saul Molina, Diana Alfonso, Mario Melo-Uribe. Centro Integral de Diagóstico, Colsubsidio, Bogotá, Colombia; Unidad Materno Fetal, Colsubsidio, Bogotá, Colombia; Universidad de La Sabana, Chia, Colombia.

Background: Fetal autopsies are essential in maternal fetal medicine. They provide information for parent guidance regarding genetics and future pregnancies. The purpose of this study, is to describe the frequency of fetal and perinatal malformations in a series of autopsies and surgical specimenes and their clinical, cytogenetical and ecography correlation.
Design: A review of fetal and perinatal autopsies, as well as surgical specimens from the pathology department of Colsubsidio in Colombia, was held between January 2005 and December 2013. Demographic, morphological and genetic variables were analyzed.
Results: Out of the 368 perinatal deaths during the studied period, 126 autopsies were made (34,2%) and 31 surgical specimens were included. The most frequent malformations found were: multiple malformations due to aneuplodies 31,2%; genitourinary malformations 17,2%; central nervous system malformations 8,3%; cardiovascular malformations 7,6%; bone and muscle malformations 7,6%; hydrops fetalis 7%; amniotic bands 5,1% and others secondary to multiple pregnancies, diaphragmatic hernia, pulmonary malformations and neonatal neoplasms.



Results from 28 amniotic fluid karyotypes were obtained. Trisomy-21/down syndrome was found in 53,6% of these karyotypes, as well as Trisomy-18 (25%), Trisomy 13 (7,1%) and other alterations (10,7%).
Conclusions: Fetal autopsies are a fundamental tool in the diagnosis of congenital malformations and complement cytogenetic and ecographic studies. The involvement of a multidisciplinary team that includes physicians from pediatric surgery, orthopedics, urology, plastic surgery, neurosurgery, psycology, materno fetal medicine and pathology, ensures better results.

21 Next-Generation Sequencing Application in a Rapid Autopsy Program

Kyung Park, Myriam Kossai, Jacqueline Fontugne, Chantal Pauli, Kenneth Hennrick, Robert Kim, Jessica Padilla, Bishoy Faltas, David Pisapia, Steven Salvatore, Brian Robinson, Andrea Sboner, Olivier Elemento, Juan Miguel Mosquera, Himisha Beltran, Mark Rubin. WCMC, New York, NY.

Background: The Institute for Precision Medicine at Weill Cornell-New York Presbyterian Hospital is established to promote personalized medicine focused on molecular diagnostics and therapeutics. When the patients with advanced or refractory cancer are referred to the Precision Medicine Clinic, they also have an option to enroll in an IRB-approved rapid autopsy program. The tissue acquired from rapid autopsy undergoes next-generation sequencing (NGS).
Design: Five rapid autopsies were performed: 3 cases of advanced castration resistant prostate cancer, one case of recurrent anaplastic ependymoma, and one case of metastatic high grade urothelial cancer. The rapid response autopsy team started an autopsy within one hour after death. Tissue from multiple sites was procured from each patient. In 2 cases, tumor was taken for organoid, xenograft and cell line development. After H&E evaluation and frozen slide annotation, extracted DNA was submitted for whole exome sequencing.
Results: The yield of extracted DNA was high (total quantity > 5ug, concentration > 27.78 ng/ul). Quality control showed intact DNA without degradation.

	PM0	PM90	PM117	PM151	PM159
Primary tumor	Prostate	Prostate	Bladder	Cerebellum	Prostate
Metastatic sites	Liver, lymph nodes	Liver, adrenal gland, bone, lymph nodes	Liver, lymph nodes	Central Nervous System including spinal cord	Brain, lung, liver,adrenal gland, testes, bone, lymph nodes
# of sites sequenced	6	5	8	3	6
DNA conc. (ng/ul)(avg)	283	43	109	87	67
DNA 260/280 Median (range)	1.90 (1.82-1.94)	1.86 (1.70-1.89)	1.87 (1.82-1.97)	1.91 (1.82-1.94)	1.92 (1.81-2.91)
DNA 260/230 Median (range)	2.16 (1.84-2.31)	0.30 (0.13-1.01)	1.70 (1.39-1.99)	1.62 (1.56-1.83)	1.57 (0.19-1.86)
Average coverage (x)	302.9	85.3	87.4	78	84.4
Average capture efficiency (%)	71.9	86.39	85.59	86.76	84.88

When tumors from different sites were compared, a cluster of mutations specific for each site was identified. Commonly seen in aggressive metastatic disease, extensive copy number variation was present.
Conclusions: Our rapid autopsy protocol illustrates application of NGS in elucidating pathogenesis and genomic evolution of metastatic tumors. The goal of this program is to maximize the amount of high-quality fresh tissue for downstream experiments and preclinical model development.

22 Respiratory Failure and Diffuse Toxoplasmosis in the Post Allogeneic Stem Cell Transplant Setting – A Difficult Diagnosis

Kseniya Petrova-Drus, Jad Saab, Steven Salvatore. New York Presbyterian Hospital – Weill Cornell Medical Center, New York, NY.

Background: *Toxoplasma gondii* causes a rare parasitic infection that can be lethal in patients after hematopoietic stem cell transplant (HSCT). While latent cyst activation and isolated cerebral toxoplasmosis (toxo) is a well-known complication in immunocompromised patients, disseminated toxo is rare, with a reported incidence of 0.1 to 6% in HSCT patients.
Design: We report 2 cases of disseminated toxo in haplo-cord allogeneic HSCT patients diagnosed at autopsy at our institution during 2013. Consents were obtained for unrestricted autopsies and performed per standard institutional protocol. Disseminated toxo was defined as histological evidence of disease in > 1 organ and confirmed by immunohistochemistry.
Results: Gross findings showed congested lungs, without focal infiltrates or consolidations. In patient 1, multiple sub-pleural plaques 0.2-0.5 cm were present. Histology showed accumulation of intra-alveolar macrophages with intracytoplasmic organisms consistent with the bradyzoite form of *T. gondii*. Areas of necrotic debris were associated with the extracellular tachyzoite form. Both forms of the parasite were present in the CNS, while only rare intracytoplasmic forms were identified in the remaining organs.

Parameter	Patient 1	Patient 2
Age/Sex	69/M	54/F
Underlying disease	MDS	T-ALL
Toxo IgG/IgM	Pos/ Neg	Pos/ Neg
PjP prophylaxis (TPM/SMZ)	Day+36	None
Symptoms	Dyspnea, diarrhea	Respiratory distress
Time from HSCT to death	Day+38	Day+32
Clinically suspected cause of death	PjP infection	CMV infection
Organs involved by toxo	Lungs, CNS, heart,adrenals, liver, kidneys, large bowel, stomach, bone marrow	Lungs, CNS, heart
Lung weight (g)	R=1420, L=1090	R=1300, L=1150
Pleural effusions (mL)	R=650, L=300	700 each

MDS, myelodysplastic syndrome; T-ALL, T-cell acute lymphoblastic leukemia/lymphoma; PjP, Pneumocystis jiroveci, TPM/SMZ, trimethoprim/sulfamethoxazole; CMV, cytomegalovirus.

Conclusions: Respiratory compromise in the post-HSCT period is most frequently associated with bacterial, fungal, or viral infections. Toxo is a rare but possibly underestimated complication following HSCT with a high mortality rate. A histologic pattern of diffuse intra-alveolar macrophages admixed with foci of necrosis should prompt consideration of this challenging diagnosis in the post-HSCT setting with unexplained respiratory symptoms.

23 Relapsed Multiple Myeloma Presenting as CNS Myelomatosis

Carrie Robinson, Patrick Malafronte, Teresa Cox. Walter Reed National Military Medical Center, Bethesda, MD.

Background: A 68-year old man with a history of IgA λ-restricted multiple myeloma was transferred to our hospital for suspected worsening disease following autologous stem cell transplant (ASCT) 4 months prior. He presented to his primary physician with diplopia, nausea and vomiting, and worsening back pain in the setting of complete bone marrow remission and negative oncology work up at day +100 from ASCT. MRI after a fall revealed multifocal epidural and intrathecal masses at T8-T11, an enhancing pituitary mass, and scattered decreased T1 signal consistent with myelomatous involvement of the calvarium. CSF cytology and biopsy of the spinal lesions showed malignant plasma cells. The patient underwent whole brain and thoracic spine radiation, but succumbed on hospital day 7. An autopsy was requested.

Design: Standard dissection of the thoraco-abdominal organ block revealed a consolidated pneumonia of the entire left lung with visceral pleural involvement by myeloma and associated diaphragmatic adhesions. Gross lesions of the axial skeleton were not identified. Gross examination of the brain and spinal cord was unremarkable. The pituitary gland was grossly enlarged and nodular. The brain and partial spinal cord were fixed in 10% formalin for 21 days.

Results: Microscopic examination of brain sections revealed diffuse leptomeningeal involvement by CD138+, λ-restricted malignant plasma cells. The cerebellum demonstrated myeloma cells tracking into perivascular spaces of the parenchyma. The pituitary showed near replacement of the neurohypophysis with myeloma. Malignant plasma cells were also identified in the lung parenchyma, visceral pleura and focally within the thyroid.

Conclusions: Neurologic sequelae of multiple myeloma are common, but usually secondary to direct extension or compression of nerve structures due to bone lesions. CNS myelomatosis is rare, with a 1% estimated incidence. It has been reported in patients with presumed complete remission of disease; several cases reported in patients who are post ASCT. CNS involvement of multiple myeloma has an invariably poor prognosis, and there is no standardized treatment approach.

Due to prior case reports of CNS involvement in presumed disease remission following ASCT and the present case with its acute and fulminant presentation, diagnostic suspicion of CNS involvement by myeloma should be routinely considered in patients with a history of myeloma and new neurologic findings on clinical exam. A complete neuropathological assessment should be included in autopsies of such patients, particularly in the setting of grossly normal CNS findings.

24 An Autopsy Study of Renal Fat Embolization Associated With Extracorporeal Membrane Oxygenation Placement

Dipti Sajed, James Stone. Massachusetts General Hospital, Boston, MA.

Background: Extracorporeal membrane oxygenation (ECMO) provides temporary mechanical circulatory support for critically ill patients with poor hemodynamics in severe cardiac and respiratory failure. Although a rise in its use is the current trend, treatment by ECMO is not without complications. Renal failure is common in critically ill patients on ECMO, and is associated with a high mortality rate. While the acute kidney injury (AKI) observed subsequent to the institution of ECMO is likely multifactorial, we sought to determine whether renal fat embolization might be a contributor to the worsening renal function observed in a subset of patients who underwent autopsy following veno-arterial (VA) ECMO placement.

Design: Nine autopsy cases (5 men, 4 women, age 49±16 years) with emergent VA-ECMO placement (four central and five peripheral) were evaluated. Routine hematoxylin and eosin (H&E) stained sections were assessed for renal fat emboli and in a subset of cases, oil red O staining of unprocessed tissue was performed. The change in serum creatinine levels from 12 hours prior to and 12 hours following ECMO placement was determined.

Results: Three of the nine VA-ECMO patients were observed to have renal fat emboli. The fat emboli group demonstrated a larger increase in serum creatinine following ECMO placement (1.15±0.58 vs 0.02±0.53, $p = 0.02$). One case also demonstrated fat emboli in the brain. The presence of renal fat emboli was not associated with age, sex, or VA-ECMO location (central vs peripheral). All three renal fat emboli cases were associated with cardiopulmonary resuscitation (CPR) prior to ECMO placement, compared with only one of the six cases without renal fat emboli ($p = 0.048$).

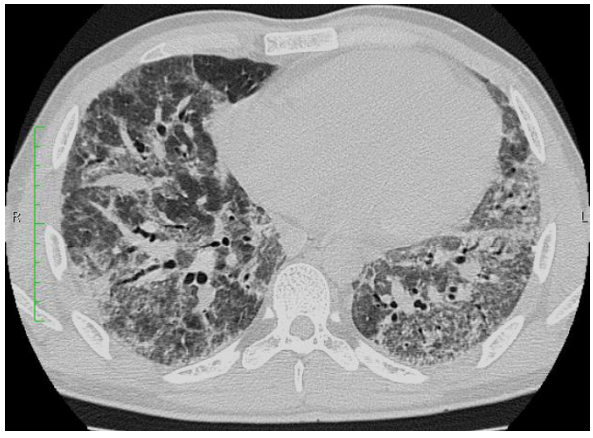
Conclusions: We demonstrate fat emboli in kidneys of three patients receiving mechanical circulatory support via VA ECMO following CPR, with a corresponding significant rise in creatinine measured 12 hours before and after ECMO placement, compared to patients with ECMO placement without renal fat emboli. We propose that renal fat embolization contributes to the acute renal dysfunction observed in a subset of patients receiving VA-ECMO treatment. The presence of renal fat emboli should be assessed in autopsies of patients following VA-ECMO placement.

25 Giant Cell Interstitial Pneumonia Triggered By Hard Metal Pneumoconiosis: A Clinic Case Presentation

Diana Marcela Sanchez Rueda, Nelson Falla Castellanos, Jose Fernando Polo Nieto, Juan Carlos Bonilla Jassair. Hospital San José, Bogotá, Colombia; Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia.

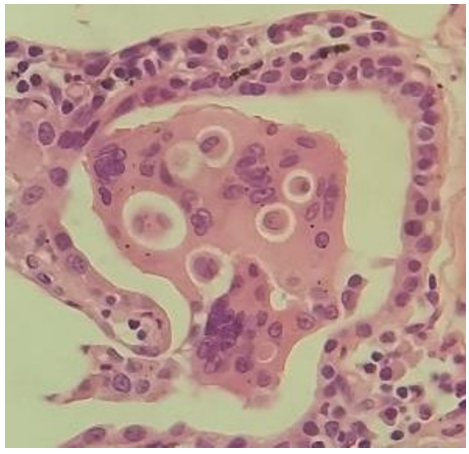
Background: Hard metal interstitial disease was described for first time in 1940 in Germany. It has a variable clinical presentation and was studied in hard metal industry workers who were followed up for 30 years. This study did not show any correlation between intensity, exposure duration, stage, and fibrosis progression. Forty-five percent of the cases had a disease progression after quitting their jobs. Therefore, it can be considered that the disease occurs after a short exposure associated with individual susceptibility which is a key player in the development of the disease, even more than dust accumulation.

Design: A 25 years-old male with medical history of pneumopathy due to tungsten exposure during 6 years, pulmonary hypertension and interatrial communication. The patient had 15 days of dyspnea, chest pain and cough with green sputum. High-resolution computed tomography showed large ground-glass fields in all lobes.



The diagnosis of chronic pneumopathy because of hard metal exposure with secondary infection was made. Inpatient care was indicated, but the patient had bad clinical evolution. For this reason, a pulmonary biopsy was done.

Results: The histology study showed an interstitial thickening in the pulmonary parenchyma due to a lymphoplasmacytic inflammatory infiltrate, presence of intra alveolar multinucleated giant cells phagocytizing macrophages, hyperplasia and atypia of type two pneumocytes (Figure 2), and vascular congestion. Also, a cyst lesion with inflammation and fibrosis was observed in the pleural wall. Special staining with Giemsa, grocott and ZN was done and the result was negative.



Conclusions: Pulmonary disease caused by hard metals is a rare occupational disease. It occurs in industry workers who handle elements made of hard metals. These metals are compound by tungsten and cobalt in their majority, but it can be added other metals which have a high hardness and hot resistance.

26 FGF23 Associated Oncogenic Hypophosphatemia/Osteomalacia in an Autopsy Case of Pulmonary Small Cell Carcinoma With Liver Metastasis

Adrienne Sauder, Renata Preira, Charvi Patel, Andrew Golden, Michael Yudd, Shahida Ahmed, Jin Choe, Victor Chang, Slawomir Sender, Donghong Cai. Rutgers New Jersey Medical School, Newark, NJ; University of California, Los Angeles, CA; Veterans Administration New Jersey Health Care System, East Orange, NJ.

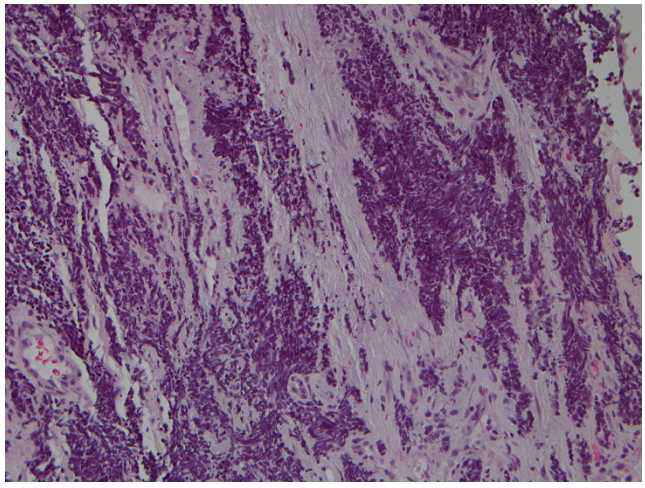
Background: Oncogenic hypophosphatemia/osteomalacia (OPO) is a rare paraneoplastic syndrome associated with phosphaturic mesenchymal tumors (PMT), which secrete fibroblast growth factor 23 (FGF23) impairing phosphate reabsorption and 1-alpha-hydroxylation of 25-hydroxyvitamin D, leading to hypophosphatemia. Here we report the first case of OPO in a FGF23-secreting pulmonary small cell carcinoma (SCC). Futhermore, the tumor cells up-regulation of Frizzled-related protein-4 (frp4) and non-phosphorylated beta-catenin, suggests involvement of the *wnt* signaling pathway in the pathogenesis of OPO.

Design: An autopsy was performed on a patient with pulmonary SCC and OPO. Imunostaining for FGF23 and beta catenin and RT-PCR for FGF23 and frp4 were performed.

Results: The lab data are supportive of OPO.

Tests	Plasma PO4	Serum FGF23	24 hr urine phosphorus	Serum 1,25-dihydroxy Vit D3	25-hydroxy Vit D
Value	0.7 mg/dL	575 RU/mL	1895 mg/dL	47 pg/ml	24 ng/mL
reference	(2.4-4.5)	(	(5-100)	(10-75)	(30-100)

FGF23 expression by tumor cells was confirmed. Comparing with cases of SCC without OPO, tumor cells were uniquely expressing high levels of cytoplasmic non-phosphorylated beta-catenin and frp4, pivotal molecules in *wnt* pathway.



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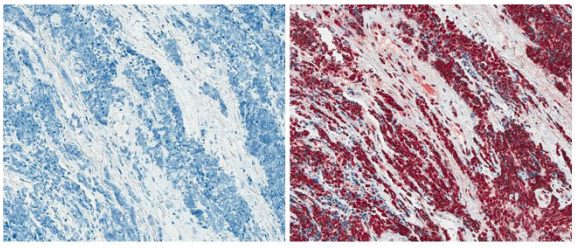

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Conclusions: This is the first report of pulmonary SCC expressing FGF23 leading to OPO. W*nt* signaling pathway is suggested in the up-regulation of FGF23.

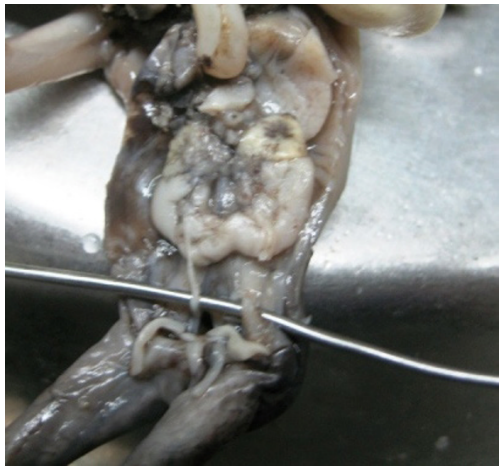
27 Utility of Autopsy in Fetuses With Congenital Renal Anomalies: The Experience and Emphasis

Sai Shalini CN, Samantha Serrao, Leena Joseph, Chitra Andrew, Swaminathan Rajendiran, Prathiba Duvvuru. Sri Ramachandra Medical College, Chennai, Tamil Nadu, India.

Background: Congenital renal anomalies(CRA) account for a significant number of perinatal deaths. Autopsy is of prime importance in all cases not only to confirm the ultrasound findings but also to categorise the anomaly according to Potters classification. Categorisation helps to determine the recurrence risk which plays an important role in counselling the patient.

Design: A retrospective analysis of all fetal autopsies received in our tertiary referral centre during the period of January 2011 to June 2014 was done. All cases of CRA were reviewed along with ultrasound findings,external,internal and histopathological examination.All autopsies done with written consent of the parents of the fetus.

Results: A total of 656 fetuses received for autopsy showed congenital anomalies in 186 cases. Of these 34(18.2%)cases had CRA. 14 cases were isolated renal anomalies,5 cases associated with Trisomy 21 and two with trisomy 18. The rest had other minor anomalies like single umbilical artery,club foot and polydactyly. We broadly categorised the renal anomalies into renal agenesis, renal morphological anomalies and congenital cystic renal diseases.Most of the cases belonged to the third category 22(64.7%) while 10(29.4%) showed renal agenesis and two cases featured horseshoe kidney. Of the 22 cases of cystic kidney,3 were of Potters type I(ARPKD),18 were of PottersType II(Multicystic dysplasia) and one was of Potters type III (ADPKD).



Among the renal agenesis cases 3 were unilateral and 7 bilateral. In 29(87.8%) of 34 cases the ultrasound observations completely correlated with the autopsy findings.

Conclusions: Fetal autopsy after termination of pregnancy or intrauterine death is of utmost importance especially in renal anomalies to arrive at a definitive diagnosis. The results of our study are in concordance with similar studies by Isaksen et al and N Kumari et al. A diagnosis of bilateral renal agenesis is important as it is a fatal condition but with low recurrence risk in future pregnancy. Histopathology gives the definite diagnosis between autosomal recessive polycystic renal disease(ARPKD) and cystic renal dysplasia which have a recurrence risk of 25% and 3% respectively.In our study post mortem examination has given a definitive diagnosis in all cases and also the associated syndromes.

28 The Mystery of the Vanishing Reinke Crystals

Sophia Smith, Scott Gilles, Juan Carlos Manivel, Hector Mesa. University of Minnesota, Minneapolis, MN; Veterans Administration Health Care Service, Minneapolis, MN.

Background: In 1896 Friedrich Reinke described Reinke Crystals (RC) in alcohol-fixed testicular Leydig cells. RC, though rare in normal testes, are found in ~1/3 of Leydig cell tumors (LCT) and are considered pathognomonic. Their function and composition are unknown. Recent studies have shown that RC are numerous in needle aspirates from LCT. In touch imprints of LCT, we observed innumerable RC not present in permanent sections. We hypothesized that the reportedly low frequency of RC in normal and neoplastic Leydig cells is due to their degradation during formalin fixation. Since RC have only been described in androgen producing cells we hypothesized that the RC may represent crystalized androgenic compounds.

Design: Testicular samples from 21 autopsy cases were collected prospectively. From each case, 5 air-dried touch imprints were stained with Diff-Quick, 5 sections were fixed and processed in 10% formalin and 5 in absolute ethanol. Fixation times varied from 1-53 days. Sections were stained with H&E for microscopic semi quantitation of RC. Immunostains for testosterone, androstenedione and dehidroepiandrosterone were used to determine if the crystals contained androgens.

Results: RC were not apparent in the cytologic preparations**.** Nineteen of 21 (90%) alcohol-fixed specimens vs 7/21 (33%) formalin-fixed specimens showed RC. The 2 alcohol-fixed specimens without RC were severely atrophic, and the patients had received finasteride and enzalutamide. The number of RC per slide varied and were arbitrarily semi-quantified as scant (< 5 per slide; alcohol (A) 6/21, formalin (F) 3/21), moderate (5-20; A: 6/21, F:3/21) and abundant (>20; A: 7/21, F:2/21). In formalin fixed specimens, RC were more numerous in specimens with short fixation times (1 day). The number of RC showed no correlation with age (61-100 yr), time from death to autopsy

(0-4 d), exposure to corticosteroids, or days of alcohol fixation (1-53 d). The alcohol fixed cases with the longest fixation times (41-53 d) showed variable degeneration of the RC. Immunostains for androgens stained Leydig cells, but not the RC.
Conclusions: RC are very common, probably ubiquitous in normal testicles, but their number is variable. They show amphiphilic properties, dissolving rapidly in aqueous solutions (10% formalin). RC are not common in cytologic preparations from normal testes, and their presence suggests the presence of a LCT. Immunostains for androgens stain specifically the Leydig cells, but not RC.

29 Age-Related EBV-Associated Lymphoproliferative Disorder With Widespread Gastrointestinal Involvement and Subsequent Development of T-Cell Lymphoma

Guldeep Uppal, Alaina Chodoff, Zi-Xuan Wang, Jeffrey Baliff, Jerald Gong. Thomas Jefferson University Hospital, Philadelphia, PA.
Background: Age-Related EBV-associated Lymphoproliferative Disorder (AR-EBVLPD) has emerged as a new subset of B-cell lymphoproliferative disorders. AR-EBVLPD is associated with a wide clinicopathologic spectrum, ranging from a benign nodal reactive hyperplasia to aggressive EBV+ diffuse large B-cell lymphoma. Here, we report a unique case of AR-EBVLPD that deviates from the characteristic progression of this disease with persistent, wide-spread gastrointestinal disease, and subsequent development of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). This is the first reported case of PTCL, NOS associated with AR-EBVLPD.
Design: A 70 year old female presented with failure to thrive and weight loss. Her clinical history was negative for any known cause of endogenous or iatrogenic immune suppression. Initial gastric and small bowel biopsies revealed severe chronic inflammation. She later presented with gastric outlet obstruction and a distal gastrectomy was performed. Histopathological examination revealed persistent chronic gastritis with a focal EBV positivity by in situ hybridization. Molecular studies revealed clonal immunoglobulin heavy (IgH) chain gene rearrangement. Over the next year, patient's clinical condition deteriorated. Repeat upper gastrointestinal biopsies were performed along with excision biopsy of a cervical lymph node. The gastrointestinal biopsies showed persistent EBV-associated LPD, polymorphic type along with appearance of atypical T-cell infiltrate. The lymph node biopsy showed features were most consistent with diagnosis of PTCL, NOS. Esophageal and lymph node biopsies showed a clonal T-cell receptor rearrangement (TCR) with identical clonal peaks. IgH rearrangement was not detected. Patient succumbed to the illness and an autopsy was performed. No palpable lymphadenopathy was detected at the time of autopsy. Examination of the visceral organs showed extensive superficial ulceration of the small bowel, distal stomach and esophagus. Esophageal and gastric biopsies revealed sheets of atypical T cells which were strongly positive for EBV.
Results: We presume that the patient's progressive clinical deterioration coincided with an increasing burden of EBV infected tumor cells. This led to altered T-cell repertoire, and the development of a malignant clonal T-cell population.
Conclusions: This is a novel case of peripheral T-cell lymphoma arising in association with an EBV-driven B cell proliferation.

30 Spectrum of Significant Liver Diseases at Autopsy in Children in a Tertiary Care Institute

Rakesh Vasishta, Pooja Murgai, Nandita Kakkar, Ashim Das, Babu Thapa. Postgraduate Institute of Medical Education and Research, Chandigarh, India; PGIMER, Chandigarh, India.
Background: To study the etiology of hepatic diseases in children at autopsy in North India.
Design: One hundred and eighty one pediatric autopsy cases, (age range 0-14 years) who presented with signs and symptoms of hepatic diseases were analyzed.
Results: Of these 66.9% were males. Metabolic disorders (38.7%) were the commonest followed by hepatitis (viral, autoimmune and others) (19.9%), infiltration by leukaemia /lymphoma (11.0%), infections (6.1%), histiocytic disorders (5.5%), vascular disorders (2.2%), extra hepatic biliary atresia- EHBA (2.2%), congenital hepatic fibrosis (1.1%), progressive familial intrahepatic cholestasis (0.6%), benign recurrent intrahepatic cholestasis (0.6%), tumors (0.6%), and other causes (12.2%).
Conclusions: Liver diseases are common in children with a male dominance. Amongst the metabolic disorders, cystic fibrosis (CF), Reye syndrome, Indian childhood cirrhosis (ICC), Galactosemia and Wilson disease were the commonest. In CF, cholestasis was seen in 6 and invasive fungal infection in 5 cases. Both classical and atypical types of ICC were noted. Predominant macrovesicular steatosis was present in 2 cases of Reye syndrome. In galactosemia, steatosis was absent in 3 cases wherein frank micronodular cirrhosis was present. Acute hepatitis was commoner than chronic. It being an autopsy study, incidence of EHBA was low.

31 Maternal Death Analysis in Japan: An Autopsy-Based Study (2011-2013)

Tomoko Wakasa, Tomoaki Ikeda, Makoto Takeuchi, Hatsue Ishibashi-Ueda, Naohiro Kanayama, Naoaki Tamura, Yoshio Matsuda, Jun Yoshimatsu. Nara Hospital, Kindai Hospital, Faculty of Medicine, Ikoma, Japan; Mie University School of Medicine, Tsu, Japan; Osaka Medical Center for Maternal and Child Health, Izumi, Japan; National Cerebral and Cardiovascular Center, Suita, Japan; Hamamatsu University School of Medicine, Hamamatsu, Japan; International University of Health and Welfare Hospital, Nasushiobara, Japan.
Background: To determine the cause of maternal death, an autopsy is essential. At autopsy, the diagnosis of amniotic fluid embolism (AFE) and pulmonary thromboembolism (PT) particularly requires careful examination. The causes of maternal death are assessed by the Maternal Mortality Evaluation Committee supported by the Ministry of Health, Labour and Welfare ever since the initiation of registration of all maternal deaths to the Japan Association of Obstetricians and Gynecologists in 2010. There were 147 cases of maternal death registered in Japan (2011-2013), with the maternal mortality rate being 3.9 per 100,000 live births as the average annual live birth count was 1039279. Of the 147 cases, 59 autopsies were performed (Autopsy rate: 40.1%); in 51 of the 59 autopsies, assessment by the Committee was completed. In this study, we analyzed all 51 registered autopsy cases (2011-2013) and classified the causes of maternal death.
Design: We analyzed all autopsy reports and medical records in the 51 cases. In suspected cases of AFE, we measured the serum levels of zinc-coproporphyrin-1 and sialyl-Tn to detect substances specific to amniotic fluid in maternal blood.
Results: In the 51 maternal deaths we analyzed, the age ranged from 23 to 42 years, with a median of 36 years. We identified 32 and 19 maternal deaths, respectively, due to direct and indirect obstetric causes. The direct causes included: AFE, 17 (33.3%); PT, 4 (8%); uterine rupture, 2 (4%); injury to birth canal, 1 (2%); atonic bleeding or DIC of unknown causes, 4 (8%); pregnancy-induced hypertension, 2 (4%); other 2 causes, 1 (2%) each. The indirect obstetric causes were: sepsis, 6 (12%); malignant lymphoma, subarachnoid hemorrhage, dissecting aneurysm of the aorta, and neurofibromatosis type I (NF-1), 2 (4%) each; other 3 causes, 1 (1%) each; and unknown causes, 2 (4%). Among the AFE cases, 13 and 4, respectively, started with atonic bleeding and cardiopulmonary collapse. Five of the 6 sepsis patients died of invasive group A *Streptococcus* (GAS) infection.
Conclusions: AFE, PT, and GAS infection were the main causes of maternal death.

Bone and Soft Tissue Pathology

32 Angiosarcoma Arising in Association With Dacron Grafts and Orthopedic Joint Prostheses: Clinicopathologic, Immunohistochemical and Molecular Analysis

Abbas Agaimy, Ofer Ben-Izhak, Thomas Lorey, Marcus Scharpf, Brian Rubin. University Hospital of Erlangen, Erlangen, Bavaria, Germany; Rambam Health Care Campus, Haifa, Israel; Caritas-Krankenhaus, Bad Mergentheim, Germany; University Hospital Tübingen, Tübingen, Germany; Cleveland Clinic, Cleveland, OH.
Background: Angiosarcoma has been rarely reported to arise in close proximity to implanted foreign material such as Dacron vascular grafts and orthopedic metal prostheses used for bone fixation or joint replacement with less than 20 cases reported to date.
Design: In this study, we provide detailed clinical and histological descriptions of 5 cases (2 new cases and 3 previously reported cases) and perform immunohistochemical and molecular analyses of all cases.
Results: All patients were males aged 50-84 (median, 71). Three received Dacron grafts and two received total hip prostheses. Angiosarcoma was closely associated with the implanted foreign material in all cases and arose within 4.6- 17 years (mean 9 years) after implantation of foreign material. Clinical symptoms were unexplained recurrent bleeding and suspected infection in the joint prosthesis cases and fatigue, weight loss and abdominal pain/symptoms in patients with Dacron graft-associated angiosarcomas. Four patients received surgical and/or palliative radio-chemotherapy. Four died of disease (range 1-24 months; mean 8 months). One patient was alive after surgery, radiochemotherapy and embolization of pulmonary metastases (last follow-up 17 months). Histologically, all tumors were high-grade with predominant solid epithelioid morphology and variable vasoformative component. All tumors expressed CD31, ERG and FLI-1, but not D2-40. Pancytokeratin expression was seen in 3 cases. TP53 was expressed in <10% of tumor cells and SMARCB1 was intact in all cases. There were no copy number alterations of *MDM2*, *CDK4* or c-*MYC*.
Conclusions: Prosthesis-associated angiosarcomas are characterized by high-grade nuclear features, predominance of solid epithelioid cytomorphology and lack of lymphatic endothelial differentiation. Absence of c-*MYC* amplification indicates a different pathogenesis compared to histologically similar secondary (radiation-associated) angiosarcomas. Likewise, absence of *MDM2* amplification in the 3 Dacron-associated cases argues against pathogenesis similar to intimal sarcoma.

33 Genomic Characterization of PEComas: Dichotomy of Genetic Abnormalities With Therapeutic Implications

Narasimhan P Agaram, Yun-Shao Sung, Lei Zhang, Chun-Liang Chen, Hsiao-Wei Chen, Michael Berger, Cristina Antonescu. Memorial Sloan Kettering Cancer Center, New York, NY.
Background: Perivascular epithelioid cell neoplasms (PEComa) are a family of mesenchymal tumors with hybrid myo-melanocytic differentiation. Although most PEComas harbor loss of function *TSC1/TSC2* mutations, a small subset were reported to carry *TFE3* gene rearrangements. As no comprehensive genomic study has addressed the molecular classification of PEComa, we sought to investigate by multiple methodologies the incidence and spectrum of genetic abnormalities and their potential genotype-phenotype correlations in a large group of 37 PEComas.
Design: RNA sequencing and Fusion seq analysis was performed on eleven tumors. RT-PCR, DNA-PCR and Fluorescence In Situ Hybridization (FISH) methodology was used to validate the gene fusions. Targeted exome sequencing using the IMPACT assay was performed on twelve tumors. Mutations were validated using Sanger sequencing.
Results: The tumors were located in soft tissue (9 cases) and visceral sites (28) including uterus, kidney, liver, lung and urinary bladder. Combined RNA sequencing and FISH analysis identified 8 (22%) *TFE3* gene rearranged tumors, with 3 cases showing *SFPQ/PSF-TFE3* fusions and one case a novel *DVL2-TFE3* fusion. The *TFE3*-positive lesions showed distinctive nested/alveolar morphology and were equally distributed between soft tissue and visceral sites. Additionally, novel *RAD51B* gene rearrangements were