United States & Canadian Academy of Pathology

Annual Meeting, Seattle, WA March 12 - March 18, 2016

PLATFORM and POSTER PRESENTATIONS

Autopsy

1 The Autopsy Findings of 116 Fetuses with Prenatally Diagnosed Central Nervous System Anomalies

Hulya Akgun, Mustafa Basbug, Figen Ozturk, Turhan Okten. Erciyes University, Kayseri, Turkey.

Background: Central Nervous System (CNS) anomalies are common congenital anomalies. The aim of this study was to compare the consistency of CNS anomalies detected by second trimester prenatal ultrasound examination with the findings in fetal autopsies following the termination of pregnancy (TOP) in the second trimester.

Design: In a 10-year long prospective study,325 second-trimester TOP was performed at a tertiary referral center, due to fetal malformation diagnosed by second trimester-ultrasound examination. Fetal autopsy was conducted on all of these cases to compare ultrasound findings with fetal autopsy findings.

Results: Following the TOP, 325 prenatally diagnosed malformed fetuses were analyzed. In addition to 113 cases already diagnosed with CNS malformations, fetal autopsy revealed 3 additional CNS malformation cases. For these 116 CNS malformation cases, the results are as below: The mean maternal age was 25 years (range 14-42). The mean gestational age at the time of termination was 20 weeks (range 14-28). CNS anomalies were isolated in 52 (45 %) of the 116 cases. Hydrocephaly (34%) and spina bifida and myelomeningocele with or without hydrocephaly (32%) were two most common CNS anomalies, followed by anencephaly (14%) and encephalocele (13%). Six cases were diagnosed corpus callosum agenesis. The other cases were holoprosencephaly (n=3), Dandy–Walker syndrome (n=2) cerebellar vermis agenesis (n= 2), lissencephaly (n=1). In 64 cases, the CNS anomalies were associated with other systems' anomalies: cardiovascular (n=20), musculoskeletal (n=19), gastrointestinal (n=12), urinary system (n=15) and fascial anomalies (n= 16). Seven cases with encephalocele had associated malformations including multicystic renal dysplasia and polydactly consistent with Meckel-Gruber syndrome. Fetal autopsy confirmed all prenatally diagnosed CNS anomalies. However, Dandy–Walker syndrome (n=3), cerebellar vermis agenesis (n= 2) and corpus callosum agenesis (n= 2) were not confirmed during fetal autopsy due to postmortem autolysis and dissection difficulties. Fetal autopsy revealed additional findings in other systems except CNS.

Conclusions: Fetal autopsy including gross and histopathological examination of CNS is important to establish a definitive diagnosis. Gross examination may point toward syndromic diagnosis like Meckel-Gruber syndrome. This study confirms that developmental anomalies of the CNS ara frequent and that ultrasound diagnoses are in concordance with the autopsy diagnoses.

2 Our Rapid Research Autopsy Program: A Solid Platform for Next Generation Clinical Trials

Prashant Bavi, Hamidreza Sharifzad, Jagdish Butany, Anthony Joshua, Michael H Roehrl. University Health Network, Toronto, ON, Canada; Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Over the last 1.5 years, we have developed a large comprehensive Rapid Research Autopsy Program at our Cancer Center. This study describes key components of the program, which allows us to ask novel questions in cancer research about molecular heterogeneity, treatment response, and escape mechanisms of tumors. The program puts pathology in the driver seat for the next generation of clinical trials.

Design: So far, 105 patients have been enrolled and studied by directed rapid ("warm") research autopsies. We studied: Tumor kinetics by integrating radiographic imaging findings and tumor burden; (2) metastases to distant organs and unusual sites; (3) presentation and metastatic spread of rare/unusual neoplasms; (4) systemic adverse effects of new targeted therapies/immunotherapy. The samples from our program are typically investigated by large-scale genome sequencing, transcriptomics, proteomics, and as living biobanks (organoids, xenografts).

Results: In our series of 105 autopsies, patient age ranged from 24 to 86 years (median, 65 years) with 57 males and 48 females; cancer types were 21 GI, 13 respiratory tract, 18 GU, 17 melanomas, 9 GYN, 8 breast, 5 heme, 2 sarcomas, and 3 ENT. A striking finding was the high incidence of cardiac metastases (23.3%) with only 2 of these cases detected by pre mortem imaging. Over 10,838 sample units were banked for research (median, 71 per autopsy): frozen tissue (3822), FFPE (3311), whole blood (689), plasma (2223), serum (188), and frozen buffy coat (605). Metastases to lung, liver and lymph nodes accounted for the top three harvested tumor samples. From 21 high value autopsies, we have been using fresh tissues (>200 samples) for live-cell immunology, xenografting (pancreas, prostate), organoids (pancreas), and ctDNA (melanoma). Stringent quality assurance steps are built in the program and the median tumor cellularity across all banked tumors was 83.2%. RIN scores showed that a high-quality RNA is obtained from tumor tissues even up to nine hours after death.

Conclusions: Striking underestimation of tumor burden by radiologic imaging was noted in virtually all patients. The high quality well annotated samples are a research gold mine for clinical trials and treatment resistance/heterogeneity research. The next generation of personalized molecularly driven clinical trials will benefit enormously from our rapid autopsy program because it will provide a unique opportunity for complete characterization of the mechanisms determining treatment response or treatment failure in clinical trials with pathology playing the key role.

3 Immune-Related Adverse Events (irAEs) Following CTLA-4 and PD-1/PD-L1 Blockade in Advanced Melanoma: A Comprehensive Rapid Autopsy Study

Prashant Bavi, Rasmus Kiehl, Oyedele Adeyi, Ozgur Mete, Carmen Avila-Casado, Hamidreza Sharifzad, Anthony Joshua, Jagdish Butany, Michael H Roehrl. University Health Network, Toronto, ON, Canada; Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Novel immune checkpoint blockade with antibodies that target cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) have shown promising results in melanoma. CTLA-4 and PD-1/PD-L1 blockade results in adverse events termed immune-related adverse (irAEs) that are poorly characterized at the histological level. The aim of this study was to comprehensively characterize irAEs.

Design: 12 advanced melanoma patients (6 male; 6 female) treated with immune checkpoint blockade were studied. A comprehensive histopathological study was done to investigate systemic side effects of immunotherapy on heart, liver, kidney, endocrine organs (pituitary, thyroid, adrenals), and CNS. We correlated observed histological changes related to irAEs with lab results and radiological imaging.

Results: Patient age ranged from 24 to 70 years (median, 59 years). The mean duration of treatment for CTLA-4 and PD-1 was 63 days and 41 days. The median time from start date of treatment with immune checkpoint blockade to death was 226 days and 191 days for CTLA-4 and PD-1/PD-L1, respectively. Features attributed to immune activation were found in the CNS, thyroid, adrenal, kidney and liver as follows: neurologic irAEs characterized by demyelination, focal perivascular lymphocytic infiltrates and presence of macrophages; endocrinopathic changes including destructive thyroiditis, variable degrees of involutional changes and focal interstitial lymphocytic infiltrate in the adrenal cortex. Granulomas from possible immune activation were found in the liver and kidney of one patient. Other findings included renal focal tubular microcalcification, tubular epithelial isometric vacuolation changes, and sinusoidal obstruction-like syndrome in the liver. None of our patients developed autoimmune hepatitis syndrome.

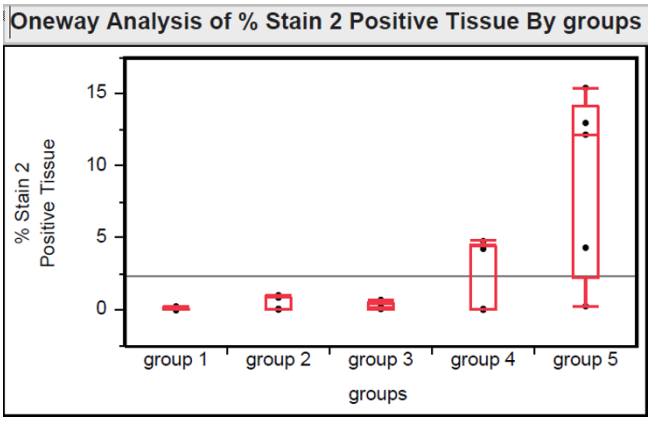
Conclusions: Little is known about histological correlates of irAEs. Preliminary results of this study suggest that irAEs may result in novel histological findings that may give insight into immune checkpoint inhibitor effects and pathogenesis. With the continuing and expanded usage of immune checkpoint blockade in various tumors, understanding their effects will be crucial to minimizing the morbidity associated with these agents. We believe this report is valuable in defining the possible multisystemic nature of these adverse effects that require clinical monitoring in patients treated with these novel agents.

4 Quantitation of Oil Red O Staining Via Digital Imaging Analysis in the Evaluation for Pulmonary Fat Embolization at Autopsy

Melissa M Blessing, Toby C Cornish, John R Lehman, Sarah M Jenkins, Joseph J Maleszewski, Marie Christine Aubry, Peter T Lin. Mayo Clinic, Rochester, MN; Johns Hopkins University, Baltimore, MD.

Background: Oil Red O staining (ORO) is often used to confirm the diagnosis of pulmonary fat emboli (PFE), a rare but important complication of blunt trauma and orthopedic procedures. PFE may also be seen in the setting of cardiopulmonary resuscitation (CPR). The threshold of ORO staining at which PFE can be considered an immediate cause of death is not well-defined. One obstacle to better defining this threshold is the inherent subjectivity in assessing the extent of ORO staining. Digital imaging analysis of ORO allows an objective quantification of PFE. To validate this method, we quantified ORO staining in lung tissue of known PFE cases and various control cohorts.

Design: 5 study groups, each with 5 cases, were created from our institutional autopsy cases based on suspected risk factors for PFE: 1) negative control without blunt force trauma (BFT) or CPR, 2) BFT with multiple fractures without CPR or survival period 3) BFT with multiple fractures without CPR but with survival period, 4) cardiac death with CPR, and 5) positive control with PFE diagnosed at autopsy. Frozen sections were prepared from formalin-fixed stock lung tissue and stained with Oil Red O. Slides were scanned at 20x equivalent (Leica Scanscope) and analyzed using the Halo Area Quantitation module (Indica Labs). The percentage of ORO in lung tissue was analyzed and groups were compared using the Wilcoxon test.
Results: A detectable amount of ORO was present in all 5 study groups, including the negative control. The median percentage of staining was less than 0.2% in Groups 1-4 and 12% in Group 5.



Group 5 was significantly different from groups 1-3 ($p<0.05$).

Groups	Median % staining	Group Comparison	p-value
Group 1	0.1529	Group 5	0.0122
Group 2	0.1028	Group 5	0.0367
Group 3	0.1529	Group 5	0.0216
Group 4	0.0946	Group 5	0.0601
Group 5	12.1755		

Conclusions: The results of this pilot survey suggest digital imaging analysis of ORO in autopsy lung tissue is a valid method for evaluation of PFE. Use of this method to evaluate a larger, more diverse cohort is underway.

5 Hematopoietic Cell Transplant: Kidney Findings at Autopsy

Brian T Brinkerhoff, Donald C Houghton, Megan Troxell. OHSU, Portland, OR.
Background: Hematopoietic cell transplant (HCT) patients may experience significant renal injury due to exposure to cytotoxic conditioning agents, immunosuppression, radiation, infection, ischemia, and graft versus host disease. We reviewed clinical and renal pathologic findings at autopsy at our single institution.
Design: The autopsy report database was searched (2009-2014) for patients with previous HCT. Forty-seven patients were identified with average age of 50.3 years (1-71 range). Patients had average post-transplant survival of 13 months (range: 1 day to 25 years, 32 deceased within 6 months). Renal pathology was reviewed on H&E, PAS and C4d stains, with fibrosis and atrophy visually estimated, and correlated with clinical data.
Results: Of the 47 patients, 40 received allogeneic HCT and 7 received autologous HCT. Pulmonary or infectious disease contributed to death in 39 patients (83%). The most prevalent renal finding was acute thrombotic microangiopathy (TMA) in 10 patients (21%); of these patients, all received allogeneic stem cells, at least 8 had calcineurin inhibitor (CNI) exposure, and 6 were conditioned with total body irradiation. Membranous nephropathy (MN) was seen in two allogeneic recipients (7 and 24 months post-transplant) detected on C4d immunostaining; both had proteinuria and hypoalbuminemia, but MN was unrecognized clinically. Other renal findings included chronic TMA, focal segmental glomerulosclerosis, diabetic glomerulopathy, amyloidosis, lymphoma, fungal or bacterial infections, glomerular silver deposition (patient ingested colloidal silver preparation independent of HCT), calcification (including oxalate). 47% of patients had interstitial fibrosis (IF) out of proportion to the degree of tubular atrophy (TA). At least moderate arteriosclerosis was present in 57%, and 51% had arteriolar hyaline (most minimally involved). A tendency toward greater arteriosclerosis with increasing patient age was found, but other vascular pathology, IF/TA, and TMA did not significantly correlate with any of the parameters below (Table 1).

Parameter	IF>TA (n=22)	IF=TA (n=25)	Acute TMA (n=10)	no TMA (n=37)
Age (mean)	50.6	50.0	42.9	52.3
Time post HCT (months)	6.2	19.5	6.2	15.2
XRT	9/22	12/25	6/10	15/37
CNI (allogeniec)	16/18	13/25	8/8	27/30

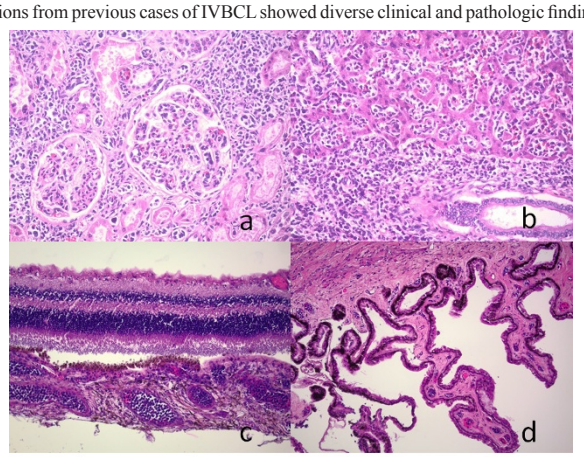
IF = interstitial fibrosis; TA = tubular atrophy; TMA = thrombotic microangiopathy
Conclusions: This study highlights substantial and varied renal pathology at autopsy of patients with previous HCT, including glomerular, vascular and tubulointerstitial pathology. In most patients, renal disorders were not clinically recognized

6 Coroner Autopsy Findings in Medical Center Quality Assurance

John B Carter, M John Spalding. Lexington Medical Center, West Columbia, SC.
Background: Coroner or Medical Examiner death investigations often involve natural causes of death related to Medical Center care. These autopsy findings are often relevant to recent medical treatments and observations, and unexpected findings are important informaton to be amplified in Medical Center QA programs.
Design: Our pathologist group has covered the coroner's autopsy service of our rural county of 200,000 since 1975, incorporating natural-cause-of-death findings into our Medical Center's QA program since 1994. As with inpatient autopsies, findings are correlated with clinical history and are reported to physicians previously involved in the patient's care. An annual QA Summary is presented to medical staff with QA recommendations--amplified learning that markedly expands the scope of autopsy surveillance. Approximately 8% of coroner autopsies showed unexpected findings which may have been of antemortem significance. Presentation of these findings, with QA recommendations has had a positive effect on patient care, with a marked decrease in complication recurrences.
Results: Coroner autopsy findings with resulting Medical Center QA recommendations over the past 20 years include:
1) Early recognition of **accidental infant suffocation** leading to community education programs seeking to prevent these tragedies.
2) Early implementation (in 1994) of **24/7 myocardial injury profiling** and chest pain monitoring protocols resulting in marked decrease in post-discharge deaths.
3) Increased recognition of **atypical presentations of acute myocardial infarction,** with marked decrease in post-MI complications.
4) Direct referral of **acute coronary syndrome** patients from primary care to emergent care evaluation, bypassing cardiologist office referral.
5) Ongoing emphasis on **atypical presentations of pulmonary embolism**.
6) The need for proactive **treatment of symptomatic Coumadin excess**.
7) The need for proactive **treatment of acute severe hypertensive episodes.**
8) The need to focus **echocardiography** on the clinically questioned abnormality.
9) The need for careful physician observation prior to discharge of **patients with acute distress complaints.**
10) Increased recognition of a variety of unexpected **drug/med interaction complications.**
Conclusions: Many health-care related deaths occur outside the hospital setting, and coroner autopsy findings in natural-cause-of-death cases can provide information valuable to Medical Center QA programs. Opportunities to amplify this information can result in decreased complication rates with life-saving potential.

7 Intravascular Large B Cell Lymphoma as a Mimicker of Susac Syndrome

Margaret Compton, Hilary Highfield Nickols, Claudio A Mosse, Stephen J Schultenover. Vanderbilt University Medical Center, Nashville, TN; Veterans Affairs Tennessee Valley Healthcare System, Nashville, TN.
Background: Intravascular large B cell lymphoma (IVBCL) is a rare extranodal lymphoma characterized by neoplastic cells within small to medium sized vessels. The central nervous system and skin are frequently affected, but any organ may be involved. The absence of lymphadenopathy and the complex and varied clinical presentation may complicate pre-mortem diagnosis.
Design: We report the autopsy of a 64 year old male who presented to care due to progressive visual changes, hearing loss, and neurological symptoms, for which he was given the presumptive diagnosis of Susac syndrome. Over the course of 10 months, his neurologic symptoms worsened. He was hospitalized two days prior to death with progressive confusion and visual loss, and was found to be in fulminant renal and liver failure. A full hospital autopsy, including sampling of the eyes, was performed. A retrospective review of our autopsy database revealed two additional cases of IVBCL.
Results: Examination of H&E stained sections revealed intravascular lymphoma within heart, lungs, GI tract, bladder, prostate, adrenals, spleen, pancreas, and bone marrow. The renal capillaries (a) and hepatic sinusoids (b) were extensively involved, corresponding to the patient's terminal course. Neuropathologic examination was significant for multifocal gray and white matter infarction with associated microvascular involvement by lymphoma. The choroidal vessels (c), optic nerve, and ciliary bodies (d) were also involved. The neoplastic cells were diffusely positive for CD20, dim positive for MUM-1, and negative for CD3. Analysis of autopsy reports and histologic sections from previous cases of IVBCL showed diverse clinical and pathologic findings.



No.	Age/Sex	Presentation
1	72/M	Multiorgan failure
2	56/M	Cognitive changes
3 (current case)	64/M	Visual, hearing, and cognitive changes

Conclusions: IVBCL may present with a variety of symptoms that may mimic vasculitis. A high index of suspicion for this entity in patients with unexplained neurologic changes or organ failure may allow for correct pre-mortem diagnosis and initiation of appropriate therapy.

8 Total Artificial Heart: An Autopsy Case Series

Craig Dunseth, Dennis J Firchau. University of Iowa, Iowa City, IA.

Background: Heart disease is one of the leading causes of death. Total artificial hearts (TAH) can be used in patients with severe biventricular heart failure as a bridge to cardiac transplant. Autopsy case reports involving TAH are sparse in the literature. The anatomy of the TAH is complex and may be overwhelming. We present an autopsy case series involving TAH at our institution including relevant anatomy and pertinent clinical and autopsy findings.

Design: A 10 year retrospective review of our autopsy database was conducted using the following terms: "total artificial heart" and "TAH." Histologic sections, final autopsy reports, and available electronic medical records were reviewed.

Results: Three TAH cases were identified; all were men aged 55-60 years who received a SynCardia TAH. All cases were previous smokers (20-60 pack years). One case had a history of nonischemic dilated cardiomyopathy. One case had a history of atherosclerotic heart disease. One case had a history of valvular heart disease. At autopsy, all cases had intact anastomotic sites, and no thrombi were identified in the TAH device. One case had infarcts of the liver, kidneys and spleen, as well as gastrointestinal ischemia; this patient died due to multi-organ failure complicating the TAH transplant and underlying heart failure. The second case died of acute Cryptococcal, Enterococcal and Escherichia coli pericarditis/mediastinitis and had purulent material surrounding the TAH with involvement of mediastinal soft tissues and chest wall. The third case died of complications of ischemic bowel related to underlying angiodysplasia of a branch of the right colic artery and had a right lower quadrant abscess, which cultured positive for Enterococcus and Candida glabrata; complications of the TAH contributed to the patient's death. The survival after TAH ranged from 13 to 182 days. Two patients died directly from complications of heart failure and TAH surgery. In the third case, complications of heart failure and TAH surgery did not directly cause death but significantly contributed to death.

Conclusions: Total artificial heart transplantation is an uncommon procedure, but due to the clinical state of those undergoing the procedure, these cases may present to pathologists at autopsy. Due to the altered anatomy and the relative infrequency in encountering these cases, they may be challenging autopsies. We present three autopsy cases with varying pathology and detailed relevant anatomy.

9 Monosomy/Trisomy 21 Mosaicism: Correlations of Karyotype to Phenotype in Multiple Tissues

Rachel Fielden, Tracy Shipe, Raymond Lewandowski, Colleen Jackson-Cook. Virginia Commonwealth University, Richmond, VA.

Background: Trisomy 21 is the most common chromosome abnormality in liveborns. Although the cytogenetic events leading to a chromosome 21 trisomic imbalance (t21) result in an equal number of cells with monosomy 21 (m21), the reciprocal outcome of m21 is rarely seen (incompatible with life). The few infants with m21 tend to have either partial m21 or mosaicism. This study's aim was to report the karyotype:phenotype findings for multiple tissues from a patient with m21/t21 mosaicism.

Design: The proband (born at 40 weeks, 5 days gestation) died at 2 weeks of age. Phenotypic findings were assessed prenatally (ultrasound), at birth, and upon autopsy. Cytogenetic studies included analyses of tissues routinely used for diagnostic testing [amniocytes (chromosomes; FISH; microarrays); and peripheral blood (chromosomes; FISH)], as well as ones associated with pathologic gross abnormalities [heart and kidneys (FISH)].

Results: At birth, the patient showed microsomia, microcephaly, dysmorphic facies, downward-slanting eyes, large dysplastic ears, left club foot, generalized hypotonia, and hypoplastic female genitalia. Additional findings seen on postmortem exam were cleft palate, a structural heart defect (ASD; biventricular hypertrophy), and a multi-cystic dysplastic right kidney. Prenatal cytogenetic analyses showed mosaicism for m21 (11%)/t21 [due to a der(21;21)(q10;q10)](89%) using chromosomes; pure m21 (100%) using interphase FISH; and m21 (47%)/normal cell mosaicism using microarrays. Postnatal lymphocyte cytogenetic studies showed a t21 [der(21;21)(q10;q10)] in 100% of cells using chromosomes and t21 (94.5%)/normal cell (5%) mosaicism using FISH. Postmortem FISH studies showed the highest percentage of m21 (96.5%) in cells from the dysplastic, multicystic right kidney. The heart showed mosaicism for m21 (62.5%), t21 (25%) and normal cells (12.5%).

Conclusions: The phenotypes of mosaicism can sometimes reflect the percentage of cells with imbalances (karyotype:phenotype correlation). Our results fit this pattern in that the most dysplastic organ (right kidney) at autopsy also had the highest proportion of m21 cells. Also, the heart had one of the highest percentages of t21 cells and showed an anomaly associated with t21. The finding of a lower percentage of m21 in blood compared to other tissues ($p<0.05$) supports the importance of testing different specimens in cases of with discrepant blood karyotype:phenotype results to enhance diagnoses and case management.

10 Digitalis Intoxication and Death from Accidental Foxglove Ingestion

Margaret Flanagan, Richard C Harruff. University of Washington, Seattle, WA; King County Medical Esaminer, Seattle, WA.

Background: Comfrey (*Symphytum officinale*) is a perennial herb of the family Boraginaceae which has leaves that resemble those of foxglove (*Digitalis purpurea*) when the plant is not in bloom. Cardiac glycoside poisoning may occur when foxglove is confused with comfrey. This case report highlights the potential risks of herb misidentification.

Design: This is an autopsy case report of a previously healthy Asian woman who accidently ingested high concentrations of digitalis. The patient mistakenly foraged foxglove (*Digitalis purpurea*) leaves that she believed to be Comfrey (*Symphytum officinale),* for use in concentrated smoothies and teas. She presented with symptoms suggestive of acute cholinergic toxicity (i.e. nausea, emesis, diarrhea, bradycardia and hypertension). Despite maximal resuscitation efforts and administration of Digibind (Digoxin Immune Fab), the patient deteriorated further and expired.

Results: The patient was a previously healthy 69-year old Asian woman who noticed "food poisoning" symptoms (i.e. nausea and vomiting) accompanied by worsening dizziness which prompted her to present to the emergency department where she was found to have acute cholinergic toxicity. Clinical history revealed that she had ingested some "Chinese tea" made from foraged leaves of a plant which was thought to be Comfrey (*Symphytum officinale),* but later confirmed to befoxglove (*Digitalis purpurea*). Electrocardiogram showed junctional bradycardia with intermittent pauses. She was found to be hyperkalemic with an initial potassium level of 6.6 mEq/L and repeat potassium level of 8.2 mEq/L. Digoxin levels were increased to 55.5 nm/mL (reference range 0.5-2.0 ng/mL). The patient remained persistently bradycardic and hyperkalemic despite maximal resuscitation efforts and Digibind (Digoxin Immune Fab) administration. She proceeded to deteriorate clinically and expired. Autopsy findings concluded the cause of death to be acute digitalis intoxication due to ingestion of Foxglove, with no indication of intent. Therefore, the manner of death was classified as an accident.

Conclusions: Foxglove (*Digitalis purpurea*) leaves can easily be confused with Comfrey (*Symphytum officinale)* when not in bloom, and if ingested, can result in cardiac glycoside poisoning. Outbreaks of Foxglove leaf poisoning associated with misidentification of herbs, have been reported in the literature. Toxicity from foxglove should be considered in patients presenting with symptoms of acute cholinergic toxicity and history of consuming foraged plants.

11 Malignant Transformation in Neurocutaneous Melanosis

Andrew Guajardo, Christopher J VandenBussche, D Ashley Hill, Miguel Reyes-Mugica, Cheng-Ying Ho. The Johns Hopkins University, Baltimore, MD; Children's National Medical Center, Washington, DC; Children's Hospital of Pittsburgh, Pittsburgh, PA.

Background: Neurocutaneous Melanosis (NCM) is a rare congenital disorder characterized by leptomeningeal melanocytic lesions and multiple, often large, cutaneous congenital nevi. While the majority of the melanocytic deposits are benign, symptomatic complications and development of malignancy can dramatically worsen prognosis. The exact mechanism and full extent of genetic abnormalities are not entirely understood; however, early developmental somatic *NRAS* mutations are implicated in the pathogenesis of NCM.

Design: We performed a complete autopsy of a 2-year-old female with NCM status post a ventriculo-peritoneal (VP) shunt, including sampling of the pigmented lesions within the central nervous system (CNS), abdominal viscera, and skin, as well as various types of normal tissue. Routine histological analyses were performed. Additionally, Copy Number Variation (CNV) analyses and targeted sequencing were performed.

Results: An autopsy revealed multiple cutaneous, CNS, and abdominal melanocytic lesions. Histology demonstrated similar benign morphology in both the skin and CNS lesions. The masses found infiltrating the abdomen showed overt malignant features including cytologic atypia and atypical mitoses. While sequencing showed a ubiquitous mutation of *NRAS* Q61R in all benign and malignant melanocytic lesions, CNV analyses elucidated a dramatic difference between the lesions. CNV showed a complex series of chromosomal gains and deletions restricted to the abdominal malignancy. Other common alterations of melanomas in genes, such as *BRAF*, *KIT*, *TP53*, *PTEN* and *CDKN2A*, were absent in both benign and malignant melanocytic lesions. Furthermore, the presence of the *NRAS* mutation in melanocytic lesions, but not in blood, normal neuroectodermal tissue, or non-neuroectodermal tissue implied that somatic mosaicism of *NRAS* is restricted to melanocytes.

Conclusions: The novel application of targeted sequencing and CNV analysis revealed not only a characteristic *NRAS* mutation in all melanocytic lesions, but chromosomal aberrations in the abdominal subpopulation of malignant melanocytes. Our finding suggests that the abdominal melanoma may have resulted from shed CNS melanocytes undergoing malignant transformation in the peritoneal cavity rather than metastasis through the VP shunt. Our case study also brings to light the mechanism of somatic mosaicism in our NCM patient and helps further elucidate the pathogenesis and potential therapeutic targets associated with this rare disease.

12 CPR-Associated Right Ventricular Rupture in the Setting of Pulmonary Embolism

Tyler Hickey, Ginjeet GK Gill, Michael A Seidman, Douglas Webber. University of British Columbia, Vancouver, BC, Canada; Vancouver General Hospital, Vancouver, BC, Canada; St. Paul's Hospital, Vancouver, BC, Canada.

Background: Cardiopulmonary resuscitation (CPR) using chest compressions is a commonly used maneuver for patients exhibiting inadequate organ perfusion secondary to cardiac dysfunction. CPR, when performed properly, is a traumatic procedure. The extent of iatrogenic trauma is variable; potentially harming a variety of tissues within

neck, thorax and superior abdomen. Certain injuries are common (e.g. rib and sternal fractures), while other injuries are rare (e.g. myocardial rupture). Here we review the frequency and types of injuries associated with CPR and describe a rare case of right ventricular rupture, secondary to CPR, identified during autopsy.
Design: Our case study examination was conducted through review of the patient records of the deceased, discussion of the sequence of events during the resuscitation with the acute clinical care team, and finally, a full autopsy and histologic examination of all relevant tissues related to the cause of death.
Results: In our case, the patient exhibited several bilateral rib fractures resultant from CPR trauma. One of these rib fractures was regionally related to a pericardial tear. Additionally, a 1 cm full thickness tear of the lower anterior right ventricle was also present, which was not regionally related to a rib fracture. A large volume of hemorrhage was present in the mediastinum and right supraclavicular area. Examination of the lungs revealed gross and microscopic evidence of acute and chronic diffuse bilateral pulmonary embolic disease.
Conclusions: CPR-related injuries are common, however, most CPR-related injuries can be managed without significant morbidity and mortality in the post-resuscitation period. There are very few described cases of ventricular rupture secondary to CPR. Of the right ventricular rupture cases described, approximately half occurred in patients with conditions causing increased right heart strain (e.g. pulmonary embolism). We propose diffuse pulmonary embolic disease, coupled with CPR, contributed to a rare occurrence of iatrogenic right ventricular rupture in this case. This case highlights both the challenges and importance of distinguishing between natural and iatrogenic injuries (e.g. CPR-related) in post-mortem pathologic assessment.

13 The Role of Rapid Autopsy as a Central Resource Available to All Researchers

Jody E Hooper, Jowaly Camacho. Johns Hopkins University School of Medicine, Baltimore, MD.
Background: In an era of personalized medicine and immunotherapy, multiple large university centers around the country are now performing autopsies on an urgent basis to collect cancer and normal tissues for understanding mechanisms of disease progression and drug resistance. Autopsy offers the unique opportunity to investigate any site encompassed by the consent, to procure tissue in large quantities from many separate bodily sites, and to sample tumors after disease resistance has occurred.
Design: All United States and Canadian rapid autopsy programs located by internet and phone searches were surveyed on their parameters of practice including organization and postmortem intervals. Given these results, we also report on the development of a new centralized program at our institution to collaborate with researchers across organ systems after many years of subspecialty rapid autopsy practice.
Results: Ten currently operating programs have been identified with three (among the most recently started) procuring all tissue types. Between two and one hundred cases per year are performed by these programs and most have twenty-four hour coverage. Autopsy consenting is completed by a wide range of providers including physicians, nurses, and program study coordinators. Between two to 95% of autopsied patients die outside of the hospital and transportation is generally performed by a transport service or funeral home and paid for by researchers, families, or the program itself.
Twelve cases have been performed to date under this new program at our institution with patient ages ranging from 10 months to 73 years, including four females and eight males. Cancer types have included prostatic adenocarcinoma, serous ovarian carcinoma, renal cell carcinoma, melanoma, pancreatic adenocarcinoma, leukemia, and three pediatric neural tumors including a case of neurocutaneous melanocytosis. Cell cultures have been successfully performed and samples are being used for xenografting. Further studies are ongoing utilizing whole genome sequencing, RNA-seq, and immunohistochemistry. Six additional patients are currently consented for rapid autopsy.
Conclusions: Rapid autopsy is a slowly but steadily growing method of cancer study with a particularly unique role to play in the evaluation and understanding of tumor genetic and phenotypic heterogeneity. Though previous practice in this area has been mostly subspecialized, centralized programs designed to collaborate with researchers in all organ systems are now becoming more prominent.

14 Novel SIX3 Mutation Leading to Holoprosencephaly

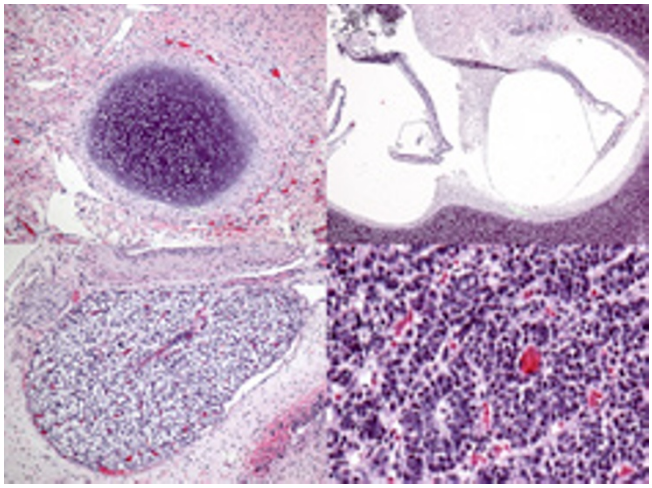
Samuel Hwang, Lindsay Taute, Michael Knapp, Christian Lanciault. Oregon Health Sciences University, Portland, OR.
Background: Holoprosencephaly (HPE) is a multifactorial developmental disorder with environmental and genetic sources that leads to the inadequate or absent midline division of a developing forebrain into separate hemispheres. HPE is the most common cause of forebrain anomalies (1 in 250 conceptuses with CNS abnormalities). Abnormal retinoic acid levels and alcohol exposure are common environmental causes of HPE, and multiple genes are found to play a role. Among these, 81 mutations of the SIX homeobox 3 (SIX3) gene have been identified in abnormal neurological and cranio-facial development. SIX3 is a transcription factor that regulates several signaling pathways involved in embryonic development. SIX3 is a direct upstream activator of sonic hedgehog (SHH) and inhibitor of wingless-type MMTV integration site family member 1 (WNT1). SHH activation and WNT1 inhibitions are necessary for dorsal-ventral patterning and establishing laterality in a developing brain. Abnormalities in SIX3 can lead to developmentally deleterious downstream effects.
Design: We present a case report with literature review of an autopsy on a 9-day-old fetus diagnosed with HPE in utero via MRI. The mother did not have any environmental risk factors for HPE. Genetic testing for mutations in SHH, SIX3 and other associated genes were performed on amniotic fluid samples.
Results: Genetic analysis revealed that the mother and child were both heterozygous for a unique SIX3 variant, where cysteine is substituted for glycine at protein position 206. Examination of the mother was negative for any phenotypic features of HPE. Autopsy findings included an undivided brain, a single anterior ventricle and the absence of olfactory and optic nerves. Examination of the sphenoid bone showed absence of the optic canal and supraorbital fissures, which may be a rare feature of this mutation.
Conclusions: The SIX3 G206C variant is a novel mutation which can lead to HPE with incomplete penetrance based on the mother's and child's phenotype. The novel SIX 3 mutation fits into the general pattern of mutations leading to HPE in this and other pathway genes. This is a highly conserved region across species and how this unique mutation could potentially affect RNA expression and protein function as well as future research to evaluate for RNA expression patterns in the SHH pathway, will be discussed.

15 The Role of Communication between Physician, Pathologist and Family in Autopsy Rate

Justin Juskewitch, Michael Paolini, Joseph J Maleszewski, R Ross Reichard, Marie-Christine Aubry. Mayo Clinic, Rochester, MN.
Background: Post-mortem examination yields clear benefits with regards to patient care, education, and research. Since the 1960s, non-forensic autopsy rates for in-hospital deaths have decreased by as much as 75%. The discrepancy between recognition of value and reluctance to obtain consent for autopsy has been attributed to barriers both perceptual and situational. We hypothesize a lack of direct communication between pathologist, clinician, and family as a contributing factor. The primary aim of this study was to evaluate a cohort of deaths (not under medical examiner (ME) jurisdiction) and assess for differences in those consented for autopsy versus not. Secondary aims included evaluation of existing communication lines and assessment of value-based metrics.
Design: Institutional databases of Mayo Clinic (Rochester, MN) were queried for all in-hospital deaths not under ME jurisdiction (June 2013-December 2013). The following data was abstracted from the electronic medical record (EMR): demography, date/time of death, autopsy-related communication (involving the patient/family, clinical team, and pathology), unanswered clinical questions at time of death, and autopsy findings. Standard descriptive and χ^2 statistics were used with a two-sided p-value<0.05 considered statistically significant.
Results: Of 372 non-ME hospital deaths, 52 (14%) consented to autopsy. There was no significant difference between the consented and non-consented cohorts in terms of age, sex, or time of death. The patient was asked about autopsy 6% of the time prior to death and the family was asked 90% of the time after death, usually by the treating physician team. Those consented were significantly more likely to have unanswered clinical questions in the EMR than the unconsented (52% vs 34%; p=0.01). Prior to performing the autopsy, 2% of cases had direct communication between the pathology and clinical teams. The majority of autopsies (54%) had an unexpected finding (most common cardiovascular or neurologic). Documentation of communication to the next-of-kin regarding preliminary and final autopsy results was identified in 6% and 40% of cases respectively.
Conclusions: Autopsy consent rates were not significantly affected by age, sex, or time of death. While those consenting to an autopsy were more likely to have lingering clinical questions, communication rarely occurred between the treating physician and pathologist. Although autopsies provided answers and unexpected findings, communication of such was usually not documented. Formal qualitative assessment of the communication between stakeholders and survey of next-of-kin satisfaction is ongoing.

16 Beckwith-Wiedemann Syndrome with Placental Mesenchymal Dysplasia in a Male (46,XY) Infant: Unique Findings at Autopsy

Annie Laib, Jerzy Stanek. University of Cincinnati Medical Center, Cincinnati, OH; Cincinnati Children's Hospital, Cincinnati, OH.
Background: Beckwith-Wiedemann syndrome (BWS) is a fetal overgrowth syndrome often presenting with: enlarged tongue/body/organs; omphalocele; ear pitting; hemihypertrophy; and placental mesenchymal dysplasia (PMD), a rare (0.02%) placental anomaly. PMD shows strong female predominance (8:1) and usually presents with: large multivesicular placenta, elevated maternal alpha-fetoprotein; fetal growth restriction. Different from partial molar pregnancy (triploid non-viable fetus, hydatid intermediate villi) and twin chorioma (diploid fetus with complete molar twin, hydatid terminal villi), PMD features a diploid viable fetus and hydatid stem villi. 25% of PMD cases are associated with BWS.
Design: We present an autopsy case of a 21-week-EGA male infant delivered by termination pregnancy due to: prenatal diagnosis of partial molar pregnancy and multiple malformations (omphalocele, cleft lip/palate, ambiguous genitalia), maternal hCG 444,862mIU/ml, and early-onset severe pre-eclampsia, despite normal 46,XY karyotype on amniocentesis. The infant died minutes after delivery.
Results: At autopsy, the appropriate-for-gestational-age infant (351.8g) showed omphalocele, small mandible, and ear pitting, but no cleft lip/palate or ambiguous genitalia. Microscopic examination revealed many findings consistent with BWS (adrenal cytomegaly, nesidioblastosis, Leydig cell hyperplasia, pituitary amphophil hyperplasia). Unexpected findings included: cardiac cartilaginous choristoma, cochlear dysplasia of the inner ear, perihepatic paraganglion, and pituitary pseudoglandular transformation.



The placenta demonstrated PMD, despite male gender, with multiple thin-walled grape-like vesicles (grossly) and hydatid stem villi with cisterns (microscopically). Fetal genetic testing confirmed 46,XY karyotype by microarray/chromosome analysis/ aneuploidy FISH.

Conclusions: This case illustrates the difficulties in prenatal differential diagnosis of congenital malformations in general, and gestational trophoblastic disease and PMD, in particular, especially in the case of a 46,XY male. This unusual case of BWS (without overgrowth features probably due to extreme immaturity) demonstrated multiple unexpected findings.

17 Comparison of Clinical Diagnoses and Autopsy Findings: 6 Year Retrospective Study

Hyejong S Marshall, Clara Milikowski. Jackson Memorial Hospital/ University of Miami, Miami, FL.

Background: The frequency of autopsies has declined in most developed countries beginning in the latter half of the 20th century. As newer diagnostic tools develop, the role of the autopsy for confirming the suspected diagnosis should be revisited and reevaluated regularly.

Design: Of 923 autopsies performed in Jackson Memorial Hospital for the last six years (2009-2014), 512 cases were of adults. Three hundred thirty-five cases were subject to review after excluding those with a short (< 1day) hospital stay (95 cases), of a single organ or a single cavity (53 cases), and cases referred from other facilities (29 cases). Autopsy reports including clinical history were reviewed by two pathologists. Medical records were reviewed if the clinical information provided in the autopsy report was unclear or inadequate. Each case was classified using the Goldman Classification.

Results: Thirty-three cases (9.9%) were identified to be Class I discrepancy where autopsy reveals discrepant diagnosis with a potential impact on survival or treatment.

Class	Number of cases (%)
1	33 (9.9)
2	32 (9.6)
3	12 (3.6)
4	110 (32.9)
5	147 (44.0)
	334 (100)

Various critical findings such as untreated infection (15 cases), pulmonary embolism (8 cases), and undiagnosed malignancy (6 cases) were found in cases of this class.

Infection		15	45.5%
	fungal pneumonia	6	
	viral pneumonia	2	
	pneumonia, NOS	2	
	menignitis	2	
	toxoplasma	1	
	candida	1	
	renal abscess	1	
Pulmonary embolism		8	24.2%
Malignancy		6	18.2%
	lymphoma	3	
	pulmonary carcinoma	2	
	gastric carcinoma	1	
Cardiovascular		3	9.1%
	retroperitoneal and/or intraabdominal hemorrhage	2	
	cartilagenous emboli	1	
Immunological		1	3%
	anaphylactic laryngeal edema	1	
		33	100%

Major significant findings which had not been clinically detected, whether clinically manageable or not (class I and II), are found in 65 cases (19.5%).

Conclusions: Despite intensive modern clinical investigations, autopsies continue to reveal major ante mortem diagnostic errors in up to 25% of cases. This study also shows a comparable result. In the light of frequent undiagnosed infections and pulmonary emboli, vigilant management for preventing these are suggested.

18 Fatal Arterial Dissections and Tears – A Retrospective Review of 42 Post-Mortem Cases

Peter Molony, Catherine Keohane, Louise Burke, Margot Bolster. Cork University Hospital, Cork, Ireland.

Background: Fatal arterial dissection, most commonly of the aorta, has a diverse range of presentations which often lead to delayed or missed diagnoses. In a condition where urgent surgical intervention may be required, this delay partly accounts for the high associated mortality of 55.8% in the first 30 days. The incidence of aortic dissection is estimated at 3 per 100,000 but with an ageing population this figure is expected to rise substantially. We present a case series of 42 post-mortems highlighting some of the more unusual presentations.

Design: The mortuary database at Cork University Hospital was searched for cases of arterial dissection over a period of 8 years. Reports on these cases were retrieved and relevant data was extracted. Cases of aortic dissection were classified according to the Stanford classification, namely type A involving the ascending aorta and/or the aortic arch or descending aorta with type B involving the descending aorta only, distal to the left subclavian artery. Where available relevant histological slides were reviewed to look for features of a vasculopathy.

Results: There was one case of spontaneous internal carotid artery dissection in a 36 year old male who presented with unilateral neck swelling and a 3 day history of sore throat and neck pain who at inquest was discovered to have had a family history of von Recklinghausen's disease. There was also one spontaneous coronary artery dissection in a post-partum female. The remaining 40 cases related to dissections and tears of the aorta. 32 were Stanford type A dissections and 8 were Stanford type B. The most common symptom was collapse (28/42) followed by chest pain (9/42). Other unusual symptoms included epistaxis, haematemesis, leg pain, limb weakness, headache and seizures. The majority of fatal arterial dissections did not present to hospital (25/42) and of those that did 82.35% (14/17) died within the first 24 hours.

Time of death in relation to admission	Stanford A aortic dissection	Stanford B aortic dissection	Carotid dissection	Coronary artery dissection
Death in community (n=25)	19	5	0	1
0-1hr post admission (n=3)	2	1	0	0
1-12hr post admission (n=5)	4	1	0	0
12-24hr post admission (n=6)	5	1	0	0
1-7 days post admission (n=3)	2	0	1	0

Conclusions: Arterial dissections continue to present diagnostic challenges with high associated mortality. We highlight some of the more unusual symptoms associated with dissection which need to be considered as part of the spectrum of presentations of arterial dissections in order to facilitate prompt investigation and lifesaving intervention.

19 Network Analysis of Placental Findings in Fetal Autopsies

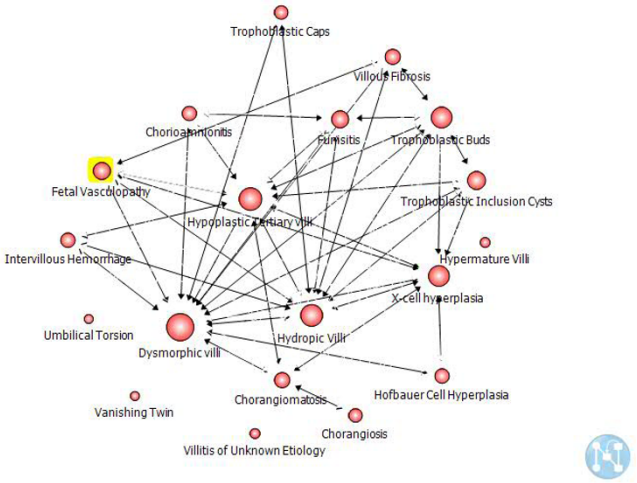
Amir Momeni Boroujeni, Derek Laskar, Elham Yousefi, Virginia Anderson. SUNY Downstate Medical Center, Brooklyn, NY.

Background: Robust placental functioning is essential to the survival of developing fetuses. We hypothesize that placental lesions in fetal autopsies follow a number of patterns.

Design: Autopsy and placental reports of all cases of intrauterine fetal demise at our institution during 2013 - 2014 were retrospectively reviewed. A network was constructed from the placental findings with each node representing a placental observation. The edges represent weighted associations between these observations. We explored the network characteristics of placental lesions.

Results: 58 cases of intrauterine fetal demise with a mean gestational age of 22.83 (14-39) were included in this study. We identified 20 significant placental lesions and 286 associations with 69 significant associations (p value < 0.01). The mean degree was 15.053. The mean power was 0.863. Dysmorphic villi, hypoplastic tertiary villi, hydropic villi, x-cell hyperplasia, trophoblastic buds, trophoblastic inclusion cysts and fetal vasculopathy had the highest power in the network (Figure 1). Cluster analysis showed clusters of highly associated placental pathologic findings. By application of gestational age for layer definition two clusters of highly associated placental lesions were identified: in the second trimester the cluster included dysmorphic villi, hydropic avascular villi, trophoblast inclusion cysts, X-cell hyperplasia and hypoplastic tertiary villi. In the third trimester the cluster included fetal vasculopathy, hypoplastic tertiary villi, chorangiosis, chorangiomatosis, increased trophoblastic buds, intervillous hemorrhage, chorioamnionitis and funisitis.

Conclusions: Network analysis is a novel method of looking at data. It is especially useful in identifying patterns and clusters. Using this approach we have shown that placental lesions associated with intrauterine fetal demise follow an identifiable pattern. More work is needed, however, to determine whether the identification of a similar pattern in the placenta of a newborn may suggest adverse outcomes.



20 "Involvement of the Liver By Primary and Secondary Malignant Tumors at Autopsy in a Cohort of Male U.S. Veterans, with Comparison to the General Population"

Aqsa Nasir, Hira Yousaf, Richard Dykoski, Juan Carlos Manivel, Hector Mesa. University of Minnesota Medical School, Minneapolis, MN; Veterans Affairs Health Care System, Minneapolis, MN.

Background: Metastatic tumors predominate over primary malignant liver tumors. In studies from different countries this ratio varies from 2.6 in Japan to 40 in USA and Europe. We performed an autopsy study at a Veterans Hospital to determine if there are significant differences between the reported frequencies in the general and the veterans U.S. population.

Design: Histologic slides and electronic medical records from complete autopsies performed between 2005-2014 at the Minneapolis VA Hospital (MN, U.S.) were searched, in compliance with institutional guidelines (Veterans Health Administration handbook 1200.05). Correlation between morphologic, immunohistochemical, and radiologic findings was performed to differentiate between primary and secondary malignancies, and to determine the primary sites of metastatic tumors.

Results: Four-hundred and five cases were retrieved. All patients were male because of the skewed population that attends Veterans Hospital. Malignant tumors were identified in 49 (12%) cases; 36 (9%) metastastatic and 12 (3%) primary liver malignancies. Metastatic to primary malignant liver tumors ratio was 3. The most common metastases were from lung (42%), pancreas (17%), and colorectum (11%). Other primary sites include; genitourinary tract (8%), upper gastrointestinal tract (5%), skin (3%), head & neck (3%), mesothelium (3%), and ileum (3%). Primary site was unknown in two metastatic cases (5%); malignant melanoma and small cell carcinoma. Adenocarcinoma pancreas (17%) was the most common histologic type of secondary liver malignancies, followed by small cell carcinoma lung (14%) and squamous cell carcinoma lung (11%). The most common primary liver malignancies were hepatocellular carcinoma (67%) and cholangiocarcinoma (17%). Remaining primary malignancies include; mixed hepatocellular & cholangiocarcinoma (8%), and angiosarcoma (8%).

Conclusions: There is a marked difference between the ratio of metastatic over primary malignant tumors among the veterans, compared to the general U.S. population. The most likely reason for this difference is the increased prevalence of cirrhosis-associated primary tumors in the veterans population due to chronic hepatitis and increased alcohol use, which are major health issues affecting U.S. veterans. Cirrhosis was present in 37 cases (9%) in our study and bridging fibrosis without cirrhosis was present in 30 additional cases (7%).

21 Architecture of Colonic Lamina Propria Stromal Cells Is Altered in Portal Hypertension

Joie Otto, Judith Aronson. University of Texas Medical Branch, Galveston, TX.

Background: Portal hypertension is associated with increased bacterial translocation across the gut wall, leading to complications such as spontaneous bacterial peritonitis and phlegmonous colitis. Intestinal lamina propria stromal cells, including subepithelial myofibroblasts, play key roles in inflammation, immune responses, and epithelial barrier function. Examining mesenchymal elements that contribute to the structural integrity of the colonic mucosal barrier may provide insight into mechanisms of bacterial translocation in portal hypertension. This study asked whether architecture of colonic mucosal stromal cells is altered in portal hypertension.

Design: Thirty-six patients with cirrhosis and thirty-eight age-matched control cases were selected from the UTMB 2011 and 2012 autopsy case files. A single, well oriented colon section from each subject was immuno-stained for alpha smooth muscle actin (SMA) and lymphatic endothelium (D2-40). After an exploratory analysis of SMA staining patterns, SMA positive cell distribution was evaluated independently by two blinded observers. Frequencies of staining patterns were compared between groups using Fisher exact test. Mucosal D240 positive lymphatics were counted according to published criteria.

Results: Compared to controls, cirrhosis cases showed increased frequency of SMA+ cells in the superficial colonic lamina propria especially in the periluminal zone. There was no difference between cases and controls in staining patterns of SMA+ subepithelial myofibroblasts around crypt bases. No differences in the density of mucosal lymphatics were identified between cases and controls.

Conclusions: Our results suggest that portal hypertension is associated with alteration in the subepithelial myofibroblast SMA expression along the colonic crypt axis, with increased SMA expression towards the luminal end. It is possible that this change could affect subepithelial sieve or innate immune functions; future studies will explore the relationship of these changes to mucosal barrier function. This is to our knowledge the first study
investigating changes in colonic stromal cells in portal hypertension.

22 Medical Renal Diseases Are Frequent but Often Unrecognized in Adult Autopsies

Marie Perrone, Anthony Chang, Kammi J Henriksen. University of Chicago, Chicago, IL.

Background: Acute and chronic renal diseases affect a significant proportion of hospitalized patients and contribute greatly to morbidity and mortality. In the US, nearly 50% of adults over age 70 have chronic kidney disease (CKD). In addition, up to 20% of ICU patients develop acute kidney injury (AKI). Patients with AKI have reported mortality rates of 10-80%, and CKD significantly increases mortality risk. Therefore, we expect a high prevalence of kidney disease at autopsy. It has been reported that non-neoplastic renal diseases are often missed in tumor nephrectomy specimens, likely due to suboptimal training in medical renal pathology. The purpose of this study is to determine the spectrum of medical renal pathology which is unrecognized in adult autopsy specimens.

Design: We identified 100 consecutive adult autopsies performed at a large teaching hospital in 2014. We omitted 35 limited autopsies that did not include the kidneys. Eight more cases were excluded because a fellowship-trained renal pathologist had reviewed the case. For the remaining 57 cases, the H&E slides were reviewed. Additional studies were obtained as necessary, including histochemical and immunofluorescence stains. Diagnoses of "mild arterionephrosclerosis" were excluded.

Results: Of the 57 cases, 21 (37%) accurately reported renal pathologic diagnoses, including diabetic nephropathy and thrombotic microangiopathy. Additional studies for findings such as mesangial sclerosis, hypercellularity, thickened basement membranes, or atypical tubular casts were obtained for 21 cases (37%). Of the 36 cases without significant reported pathology, 9 cases (25%) were found to have missed diagnoses, including diabetic nephropathy (3), thrombotic microangiopathy (2), light chain cast nephropathy (1), amyloidosis (1), endocarditis-associated glomerulonephritis (1), and oxalate nephropathy in a patient with Crohn's disease (1). 2 of 10 cases originally reported as "autolyzed" had significant missed diagnoses (cast nephropathy and diabetic nephropathy).

Conclusions: This study demonstrates that medical renal diseases are common in autopsy cases, but significant diagnoses can be easily overlooked. Our understanding of how renal disease contributes to morbidity and mortality would benefit from increased recognition of renal diseases in autopsy specimens. The Accreditation Council for Graduate Medical Education included the requirement of renal pathology in the anatomic pathology curriculum for pathology residents effective July 1, 2015 and this may provide one solution for this knowledge gap.

23 The Final Timepoint of Disease Progression: Rapid Autopsy in the Precision Medicine Era

David Pisapia, Steven Salvatore, Chantal Pauli, Joanna Cyrta, Robert Kim, Bishoy Faltas, Jeffrey Greenfield, Brian D Robinson, Andrea Sboner, Olivier Elemento, Himisha Beltran, Mark Rubin, Juan Miguel Mosquera. Weill Cornell Medical College (WCMC), New York, NY; WCMC, New York, NY.

Background: The Englander Institute for Precision Medicine has been established to promote personalized molecular diagnostics and therapeutics. Patients may also elect to enroll in our rapid autopsy program. Logistics are in place for patients who may die in a range of settings including for in-house patients and those in remote hospice care settings. Tissue acquired from rapid autopsy undergoes next-generation whole exome sequencing (WES) and is harvested for tumor organoid development and cell culture.

Design: Eleven rapid autopsies have been performed thus far including seven adult patients with metastatic disease:
- 3 cases of prostate carcinoma,
- 2 cases of urothelial carcinoma,
- 1 case of renal cell carcinoma,
- 1 case of ovarian serous carcinoma;

and four pediatric gliomas including:
- 2 cases of anaplastic ependymoma,
- 1 case of gliomatosis cerebri, and
- 1 case of diffuse pontine intrinsic glioma.

Post-mortem time interval was as short as one hour for inpatients. Tissue samples were frozen from each patient and harvested for organoid, xenograft and/or cell line development. After H&E evaluation of frozen material, DNA was extracted for WES from multiple tumor sites and normal samples from each patient.

Results: To date, 231 frozen tumor samples were procured from 76 independent anatomical sites over 11 cases. Of the sequenced samples to date, the average DNA concentration obtained was 127 ng/uL. Tumor organoid development of ovarian carcinoma was achieved from a patient who died outside of the hospital. In one case of ependymoma, rapid autopsy permitted collection as a final timepoint in a disease for which 8 prior surgical specimen timepoints are available to study tumor evolution.

Conclusions: With streamlined logisitics, we have shown that it is possible to obtain high quality autopsy tissue from a diversity of primary and metastatic sites for WES of tumor and normal samples, even from patients who die outside of the hospital. In further

work, we will utilize this valuable resource to study tumor evolution and clonality, the relationship of primary and metastatic disease, and response to therapy. Indeed, rapid autopsy affords a critical window into the evolution and final stages of a patient's disease.

24 Different Strokes for Different Folks: A Case Series of Abdominal Apoplexy

Varsha Podduturi, Joseph M Guileyardo. Southwestern Institute of Forensic Sciences, Dallas, TX; Baylor University Medical Center, Dallas, TX.

Background: Abdominal apoplexy (AA) or idiopathic spontaneous intraperitoneal hemorrhage is a rare and usually fatal condition that results from various conditions affecting the arterial and venous abdominal vasculature. This diagnosis excludes abdominal hemorrhage caused by ectopic pregnancy, aortic aneurysms, and visceral malignancies. AA may occur from various points, including second or tertiary branches of the abdominal aorta.

Design: We describe clinical, pathologic, and autopsy findings of 4 AA cases. Each case had an autopsy report and H&E slides. Clinical data was extracted from medical records.

Results: The 4 cases include 3 women and 1 man ranging from 33-70 years of age. Three patients had multiple co-morbidities. There were varying degrees of hemoperitoneum. H&E sections found transmural disruptions of the gastroduodenal artery (two cases) and splenic artery (one case), and rupture of the superior mesenteric-portal venous system with perivascular pseudo-aneurysm formation (one case).

Case	Age/ Sex/ Race	Procedure	Hemoperitoneum at Autopsy (mL)	Aneurysm Site	Other Autopsy Findings
1	70/F/ White	None	700	Gastroduodenal artery	Hypertensive and atherosclerotic cardiovascular disease
2	55/F/ White	Attempted vascular ligation	5100	Rupture of superior mesenteric-portal venous system wiwth perivascular pseud-aneurysm formation	None
3	59/F/ Black	Paracentesis X2	5900	Gastroduodenal artery	Cirrhosis, hepatocellular carcinoma, uterine leiomyomata, lipid cell tumor of left ovary, chondroid hamartoma or left lung
4	33/M/ Latin	None	1200 clot; 1670 liquid blood	Splenic artery	Cardiomegaly (590 grams), mild atherosclerosis

Conclusions: Cases of hemoperitoneum are challenging at autopsy for many reasons. The lack of intravascular pressure, the small size of the vascular disruption, and the fact that relevant anatomic structures are obscured within a bloody field, may render finding a source of bleeding difficult, if not impossible. Accurate diagnosis may require careful preservation of the specimens with histologic sampling before the source of bleeding can be confirmed. A high index of clinical suspicion is warranted since early diagnosis and surgical intervention are critical in improving prognosis, and non-operative mortality approaches 100%. Furthermore, accurate postmortem diagnosis may have profound medico-legal implications, which is illustrated in case #3 in which clinicians thought that the paracentesis procedure contributed to her demise.

25 Pulmonary Emboli and the Risk of Mortality in a Diverse Disease Environment

Maryam Shabihkhani, Jody E Hooper. Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Venous thromoembolism (VTE) and pulmonary emboli (PE) are more common than any other cardiovascular disorder besides myocardial infarction and stroke. Between 10 and 30 percent of patients with venous thromboembolism (VTE) die within 30 days of onset and approximately a quarter of pulmonary emboli (PE) present with sudden death. Though PE is readily associated with malignancy and other illnesses which create difficulty with mobility, there may be greater association risk with other types of disease than has been previously documented.

Design: Autopsy records for the last twenty years at our institution were retrospectively searched for the term "pulmonary embolus". For cases identified with PE as the cause of death, age, gender, race, death location (in or out of hospital), VTE and PE history, prophylaxis, history of surgery or mobilization, and other significant morbidities were recorded.

Results: PE was listed as the cause of death at autopsy in 48 cases. The average age was 58.4 years with ages ranging from 14 to 94 (two patients with unknown dates of birth). There were 30 white decedents, 17 were black, and one was Asian. There were 29 men and 19 women. Only 10 decedents had a documented history of prior DVT or PE and 9 of these patients were undergoing some type of prophylaxis. All patients but one had concurrent disease and that one died from a car accident outside of the hospital. There was a history of malignancy in 13 patients and 6 had neurologic or musculoskeletal disorders affecting mobility. Disease in the remaining patients varied widely in type and severity, with the next most common category of complaint being cardiac (history of myocardial infarction, hypertrophy, and congenital heart disease). Three patients had prior organ transplants and two had undergone recent surgery. Fourteen patients had hypertension and nine had diabetes. Fourteen patients (27%) died of PE outside of the hospital; five of these had malignancies and three had neurologic disorders, leaving 42% with conditions which may not usually be associated with direct risk for PE.

Conclusions: Over a twenty year period, male and female patients across a wide range of ages showed PE as a cause of death at autopsy. A minority had a prior history of PE and only 38% overall had concurrent morbidities of types traditionally associated with risk for PE. Greater attention to prophylaxis in patients with a variety of diseases may be warranted, particularly in an outpatient setting where patients are not being monitored.

26 Malignant Tumors Associated with Breast Cancer: Analysis of 164,211 Autopsy Cases in Japan

Yukiko Shibahara, Yumi Sugawara, Yasuhiro Miki, Yasuhiro Nakamura, Ichiro Tsuji, Hironobu Sasano. Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

Background: Breast cancer patients tend to harbor an increased risk of developing other malignancies following the diagnosis but the decreased risks of developing malignancies have not been well explored. Therefore in this study we attempted to clarify the increased and decreased incidence of cancers in breast cancer patients using autopsy cases registered in Japan.

Design: 164,211 autopsy cases in the Annual of Pathological Autopsy Cases in Japan from 2002- to 2010 were analyzed for multiple primary cancer (MPC). Among these cases, female multiple primary cancer cases (4,222 cases) were selected. We evaluated what other malignancies detected in MPC cases and the increased and decreased cancer incidence in these patients. Chi- squared test was used for analysis. All P-values were two-sided, and differences at $P < 0.05$ were considered statistically significant.

Results: Breast cancer associated MPC presented with a significantly increased incidence of ovarian, pancreatic, and skin cancer (OR [95% CI] = 1.464 [1.03, 2.08], 1.414 [1.08, 1.85] and 2.092 [1.28, 3.41]), and a significantly decreased incidence of colorectal and cervical cancers (odds ratio [OR] [95% confidence interval (CI)] = 0.732 [0.60, 0.90], 0.605 [0.38, 0.96]). A decreased incidence of colorectal cancer was detected particularly among breast cancer associated MPC aged over 60 years at demise.

Conclusions: This study is the first study to analyze large autopsy database on MPC. A significantly increased incidence of malignancies in breast cancer associated MPC cases was consistent with the results of previous population-based studies, indicating that autopsy reports could provide new clinical and pathological information data basis for the prognosis of breast cancer patients. In addition this is the first study to demonstrate the decreased incidence of colorectal cancer development among elderly breast cancer patients, suggestive of a different mechanism of estrogen actions between these two malignancies influenced by estrogens.

27 Autopsy Review of Neonatal Deaths by Disseminated Herpesvirus Infection

Emily A Sloan, M Beatriz Lopes, Robin LeGallo. University of Virginia, Charlottesville, VA.

Background: Neonatal herpes simplex virus (HSV) infections cause significant morbidity and mortality. The disseminated form of disease often presents as a sepsis syndrome consisting of pneumonitis, hepatitis, and disseminated intravascular coagulation (DIC) with multiorgan failure; these non-specific symptoms may hinder early diagnosis and treatment. Here we report on the clinical and histopathologic findings of neonatal HSV infections as determined by autopsy at a single institution.

Design: Departmental files from 1997-2015 were searched for pediatric autopsies with HSV infection as the cause of death. Presenting symptoms, time course of disease, gross and microscopic findings, immunohistochemistry (IHC), and microbiologic culture results were evaluated. Maternal labor and HSV infection histories were obtained from electronic medical records.

Results: Five neonatal deaths due to disseminated HSV were identified. Mean ages at presentation and death were 3.4 days (range 0-6) and 7.2 days (range 1-10), respectively. All births were spontaneous vaginal deliveries. Known primary maternal HSV infection was uncommon (1/5); in one case primary paternal infection was documented 2 weeks prior to birth. Frequent presenting symptoms included respiratory distress (4/5) and lethargy (3/5). Autopsy revealed desquamating (1/5) or petechial (1/5) skin lesions in a minority of cases. Microscopic examination demonstrated hemorrhagic pneumonitis in all cases, while 4 showed fulminant hepatitis and adrenal necrosis with cytopathic change. IHC stains for HSV-1 and -2 were strongly positive in these organs, confirming infection. A minority demonstrated splenic (2/5) and esophageal (1/5) necrosis with IHC positivity. Central nervous system (CNS) findings included subarachnoid (3/4), intraparenchymal cerebellar (2/4), and brainstem (1/4) hemorrhages, and white matter infarction and polymicrogyria (1/4). Post-mortem HSV cultures were positive in 3 cases [lungs (2/5), liver (1/5)]. In one culture-negative case, subsequent HSV-PCR of formalin-fixed paraffin embedded lung tissue was positive.

Conclusions: In five infants, disseminated HSV infection presented within the first week of life with multiorgan failure and DIC. Autopsies demonstrated extensive hepatic, pulmonary, adrenal and CNS involvement with confirmatory IHC. Skin lesions and known maternal HSV infection were uncommon. Recognition of HSV infection is paramount for early detection and treatment in the neonatal period.

28 Cardiac Conduction System Pathology in the Hospital Setting: A Selection of Cases

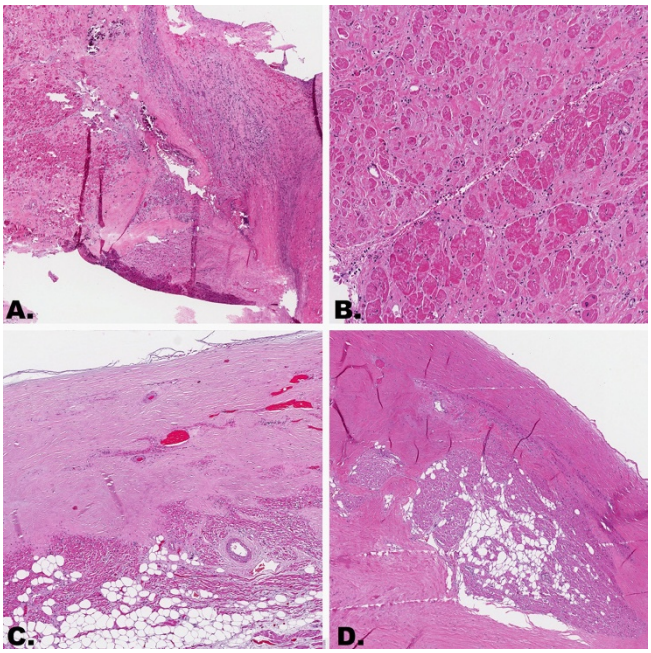
Michelle Stram, Jeffrey Nine. UPMC Presbyterian, Pittsburgh, PA.

Background: Cardiac conduction system (CCS) examination helps in evaluation of sudden unexpected death, particularly in a forensic pathology setting. In the hospital autopsy settting the CCS is not often examined since sudden unexpected death is rare. Regardless, a wide range of pathologies can affect the CCS in hospital patients, many

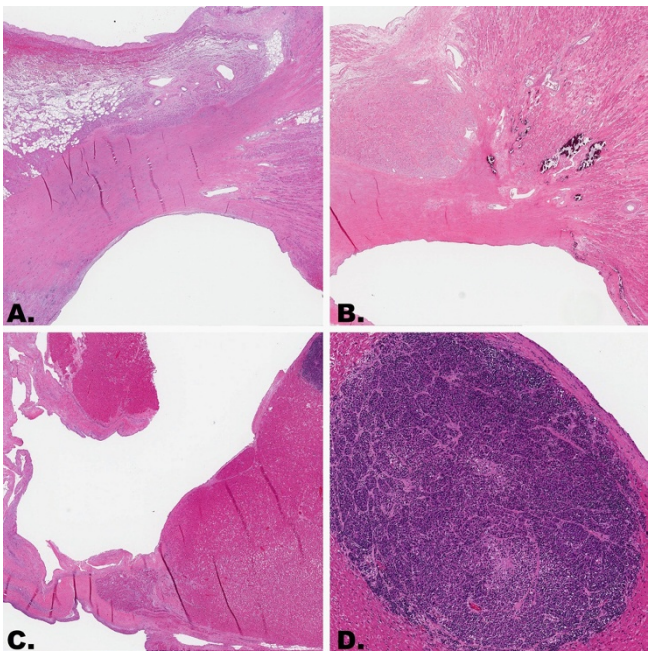
of which can cause or contribute to death. Pathology residents are progressively getting less training in autopsy, and many of the specialized examination techniques such as CCS examination are falling by the wayside. Residents would benefit from baseline familiarity with the CCS and exposure to a broad range ofCCS pathology they may encounter in the hospital.

Design: A review of 536 adult autopsies performed between 2013 and 2015 was conducted at a large academic medical center. In 20 cases histologic evaluation of the AV nodal region was performed. Among these, 13 cases of AV nodal pathology were identified and 7 cases in particular are presented in detail.

Results: Over 2-1/2 years of autopsy data, 4% of cases reviewed involved evaluation of the CCS. The demonstrated cases represent a range of CCS pathology:



A. degeneration of the AV node associated with a surgical patch, B. AV node infarct from thrombosis of the AV nodal artery, C. sarcoid infiltration of AV node, D. AV node adiposis.



A. AV node hemorrhage following extraction of an AICD lead, B. AV node calcifications, C-D. melanoma metastatic to AV node region

Conclusions: Familiarity with evaluation of the CCS is undervalued in the education and training of pathology residents. The cases delineated here represent a range of pathologic findings residents should be able to evaluate. Considering cases like these will help educate residents about the role of proper CCS examination. Encouraging resident involvement in evaluation of both abnormal and normal CCS will allow them to develop and apply the optimal techniques of dissection, and subsequently teach CCS dissection to others.

29 Retropleural Hypertension: A Probable Cause of Descending Thoracic Aortic (DTA) Occlusion in a Traumatic DTA Tear

Melissa Van Dellen, Zulfiqar Cheema, Gregory Wolfe, Clarke Stout. University of Texas Medical Branch, Galveston, TX.

Background: Traumatic DTA tears cause up to 15% of road accident deaths, mainly from rupture into the left pleural space. They also may heal with false aneurysm formation or undergo traumatic dissection (TD) with occlusion of the DTA. TDs require the more time consuming brachial artery stent deployment thus increasing the risk of death from downstream ischemia. We present an apparent TD case in which autopsy and CT scan findings indicated DTA compression by a retropleural hematoma pressurized by blood pumped through the DTA tear. The CT findings also were consistent with dissection, but none was found microscopically.

Design: This 31 year old male presented 1.5 hours after a motorcycle crash with progressing paraplegia due to DTA occlusion. Emergent CT scan with contrast revealed a DTA tear with a TD and about 1.5 liters of hematoma in contiguous mediastinal, retropleural, retroperitoneal and left renal subcapsular spaces. BP was 154/98, P 140, hemoglobin 14.6 g/dL and pH 7.17. Stenting via the brachial artery sealed the tear and restored DTA flow 2 hours later, but the patient expired from progressive acidosis and multiorgan failure.

Results: Autopsy confirmed the 4.5 cm DTA tear opposite the ligamentum arteriosum and the various hematoma sizes. The 5 cm in diameter hematoma around the DTA was denser and more homogeneous than the others, presumably due to more flow. Movat's pentachrome stain confirmed the absence of aortic dissection or other aortic disease. Fluid gushing from the nicked left renal subcapsular hematoma was our first clue that the extravascular hematomas were pressurized.

Conclusions: Sagittal images of the 8-10 cm DTA revealed a tight luminal stenosis that gradually expanded distally. Fainter dye collections along the outside of the DTA wall tapered in the opposite direction. Serial coronal images revealed a thin tri-bladed propeller-like lumen at its maximally stenotic site that gradually enlarged and became round and solid distally. The DTA wall was crinkled snugly around the propeller blades. A normal DTA was filled loosely with paper towel strips, wrapped snugly with string, fixed in formalin and cross sectioned to reveal a similar propeller shaped lumen and crinkled wall. These findings indicate that traumatic DTA tears with TDs might be stented safely via the femoral artery.

30 Next Generation Sequencing (NGS) Solves Autopsy Mystery of Metastatic Poorly Differentiated Malignancy

Laura Warmke, Austin Wiles, Catherine I Dumur, Melissa J Contos, Steven Smith. Virginia Commonwealth University Health System, Richmond, VA.

Background: Melanoma is a highly malignant disease with increasing incidence. Diagnosis of metastatic melanoma can be challenging as melanoma commonly mimics other diseases and can lose expression of characteristic melanocytic markers. Molecular analysis can help to distinguish metastatic disease.

Design: We present the autopsy findings of a 54-year-old male recently diagnosed with a well-differentiated melanoma on his back (Breslow's depth 5.12 mm) with a positive sentinel lymph node biopsy status post wide excision and left axillary dissection. After two months, he presented in renal failure, with worsening respiratory function and a large chest wall mass with peau d'orange findings suggestive of inflammatory carcinoma. Both a left chest punch biopsy and pleural fluid analysis showed a poorly differentiated malignancy with extensive lymphangiitic growth, pancytokeratin and CK7 expression, and negativity for S-100, SOX10, HMB45 and MelanA. Despite medical treatment, the patient died 3 weeks following his admission.

Results: Autopsy examination revealed diffuse involvement by an infiltrating poorly differentiated malignancy. The following systems were involved: heart, bilateral lungs, mesentery, liver, bilateral kidneys, para-aortic lymph nodes, and left chest wall (skin, soft tissue, and bone). As with the ante mortem samples, the poorly differentiated malignancy stained positively for pancytokeratin and cytokeratin 7. CK20 and CD45 were negative. Before the patient's demise, samples of both the left chest wall biopsy and the patient's original melanoma were submitted for ampliseq-based targeted next-generation sequencing (NGS) analysis to assess the mutational status of 7 cancer-relevant genes. Both samples were positive for the pathogenic BRAF V600E mutation and were heterozygous for the benign EGFR SNP rs1050171.

Conclusions: The fact that the same mutational profile, including the pathogenic BRAF V600E mutation, was found in the patient's left chest lesion and in the patient's original melanoma, supports the interpretation of the poorly differentiated malignancy as metastatic melanoma with phenotypic transformation. Somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) have been identified in 40-60% of melanomas, and 90% of the BRAF mutations occur in exon 15, resulting in the p.Val600Glu substitution (V600E). The conserved BRAF mutation helped to confirm the diagnosis of metastatic melanoma despite the metastatic disease's loss of melanoma markers and aberrant keratin expression.

31 Eosinophilic Myocarditis Is a Relatively Common Cause of Sudden Cardiac Death Due to Myocarditis

Yang Zhang, Allen P Burke. University of Maryland, Baltimore, MD.

Background: Myocarditis is a rare cause of sudden death, but a relatively common finding during forensic autopsies. We assessed the degree and type of inflammation and extent of necrosis in a series of natural deaths, and compared histologic features to clinical findings and frequency of other potential causes of death.

Design: There were 67 cases of natural death with a diagnosis of myocarditis retrieved over a 10-year period. The cases were classified into limited inflammation (multifocal or sparse, without confluent infiltrates) without necrosis (n=24, group 1), limited

inflammation with necrosis (n=23, group 2), and diffuse inflammatory infiltrates with multifocal necrosis (classic myocarditis, n=20, group 3). Other potential causes of death included pneumonia, seizure disorder, sarcoidosis, cancer, and heart disease.
Results: The mean age of group 3 (24 ± 18 years) was significantly lower than groups 1 and 2. There was no significant gender difference across groups (total 27F, 40 M). The mean heart weight was lowest (330 grams) in group 3 (p=0.09). The mean extent of infiltrates (p=0.02) and degree of myocyte necrosis (p=0.05) correlated inversely with the presence of other potential causes of death. Eosinophils were present in 21 cases (31%), and were most frequent in group 1, although there 7 group 3 cases with eosinophils (necrotizing eosinophilic myocarditis). Lymphocytes (n=22), macrophages (n=12), and neutrophils (n=12) were the predominant cell types in the other cases, with 9, 3, and 1 case(s) respectively in group 3. There was no significant differences rates of drug exposure and predominant cell type (overall 58%), although lymphocytic myocarditis was most frequently associated with antibiotic use, and neutrophils with neuroleptic drug use.
Conclusions: We conclude that the extent of infiltrates and myocyte necrosis are greatest in sudden death without other potential cause. Diffuse necrotizing eosinophilic myocarditis represented an unexpectedly high proportion of diffuse myocarditis, but was often not associated with a specific drug etiology.

32 Distribution of Lesions in Sudden Unexpected Deaths by Sarcoidosis

Yang Zhang, Allen P Burke. University of Maryland, Baltimore, MD.
Background: Sarcoidosis is a multisystem disease of uncertain etiology that may be responsible for sudden and unexpected death. There are few autopsy series of patterns of multisystem involvement by sarcoidosis. We herein characterize a series of sarcoidosis from a single medical examiner's office to study the distribution of lesions in sarcoidosis and correlate distribution with clinicopathologic parameters.
Design: A retrospective search of sudden sarcoidosis death was performed from a state-wide medical examiner system over 11-year period. Extent of disease and clinical history was correlated with cause of death. There were 29 sudden deaths due to sarcoidosis identified.
Results: Of the 29 cases, 25 deaths were caused by cardiac sarcoidosis with a presumed mechanism of cardiac arrhythmias. There were 4 deaths due to pulmonary sarcoidosis. These 4 cases of pulmonary sarcoidosis presented with massive lung involvement resulting in pulmonary failure, associated pneumonia, meningeal involvement, and the presence of cocaine in the urine. Lung involvement was also grossly present in 20 of 25 cases of sudden cardiac deaths. Of the 29 cases, 21 (72.4%) patients were clinically undiagnosed. A history of sarcoid was elicited in 6/25 (24%) of cardiac deaths and 2/4 (50%) of the pulmonary deaths. In our study, grossly evident sarcoid with histologic granulomas was also present in lymph nodes (n=17), liver (n=11), kidneys (n=7), spleen (6), and brain (n=3). Cardiac distribution involved the left ventricle in 44%, right ventricle in 44%, and epicardium in 40% of the cardiac sarcoidosis cases. At least 3 organs were involved in 66%, and 2 organs in 90% of the cases.
Conclusions: The current study of fatal sarcoidosis shows that in a medical examiner's population, most cases are due to cardiac involvement. Interestingly, most cases also had pulmonary involvement, even though the small group of pulmonary deaths did not show gross cardiac disease. However, in both groups, extensive involvement of other organs was typical. There is a high rate of cardiac involvement in forensic series because of a bias towards unexpected arrhythmic deaths; related to this is a lower rate of prior history of sarcoidosis in cardiac vs. pulmonary deaths.

Bone and Soft Tissue Pathology

33 NTRK1 Associated Gene Fusions in Pediatric Fibroblastic / Myofibroblastic Neoplasms: A Molecular Study of 58 Cases

Narasimhan P Agaram, Lei Zhang, Yun-Shao Sung, Chun-Liang Chen, Catherine Chung, Christopher Fletcher, Cristina Antonescu. Memorial Sloan Kettering Cancer Center, New York, NY; The Hospital for Sick Children, Toronto, ON, Canada; Brigham and Women's Hospital, Boston, MA.
Background: The spectrum of pediatric fibroblastic and myofibroblastic soft tissue tumors includes a number of locally aggressive neoplasms with sometimes overlapping morphology, such as myofibroma/myofibromatosis (MYO), lipofibromatosis (LPF), fibrous hamartoma of infancy (FHI), and calcifying aponeurotic fibroma, among others. As no prior study has carried out a comprehensive genetic investigation in this group of tumors, we applied the latest whole transcriptome sequencing for better molecular classification and to evaluate potential shared pathogenesis.
Design: RNA sequencing and FusionSeq analysis was performed on 9 cases (4 LPF, 1 FHI and 4 MYO) for novel fusion gene discovery. Validated fusion candidates by RT-PCR were then screened using FISH in a large cohort of cases.
Results: 58 cases were selected - 28 LPF, 11 FHI and 19 MYO. RNA sequencing identified gene fusions in 3/9 cases: 2 LPF showed *TPM3-NTRK1* and *EWSR1-SMAD3* fusions and 1 MYO a *TPR-NTRK1* fusion. The 2 *NTRK1*-rearranged cases showed strong expression for NTRK1 by IHC. Further screening by FISH showed another LPF with *TPM3-NTRK1* fusion, while 18 additional LPFs displayed recurrent complex FISH abnormalities at the 1q22-23.1 locus (that includes *NTRK1* and a number of known *NTRK1*-fusion partners in other cancers). Ten of 11 FHI cases showed recurrent abnormalities in the same 1q22-23.1 region. In contrast only 2 additional MYO cases (2/18) showed 1q22-23.1 FISH abnormalities. No additional *EWSR1* gene rearrangements were identified in 7 cases tested.
Conclusions: Our results show recurrent *NTRK1* related gene fusions in a subset of LPF and rare MYO lesions. The high rate of 1q22-23.1 locus FISH alterations spanning the *NTRK1* gene in both LPF and FHI suggests the possibility of recurrent intra-chromosomal fusions / regional abnormalities. These alterations require a higher resolution methodology for more detailed characterization.

34 Primary Adult Skeletal Osteosarcoma: A Clinicopathological and Molecular Study

Deepu Alex, Lu Wang, George Jour, Sumit Middha, Raghu Chandramohan, John Healey, Khedoudja Nafa, Meera Hameed. Memorial Sloan Kettering Cancer Center, New York, NY.
Background: Osteosarcoma is the most common primary skeletal sarcoma with bimodal age distribution occurring in adolescents (10-14 years) and older individuals above 40 years. Compared to pediatric osteosarcoma, it has been reported that adult skeletal osteosarcoma (>19 years) has a worse outcome. Herein, we investigate the clinicopathological and molecular features of a series of primary adult skeletal osteosarcomas and explore potential morphological and molecular parameters that may affect outcome.
Design: 18 cases of primary adult skeletal osteosarcomas were retrieved and reviewed. Clinical history and follow up were obtained through electronic record review. DNA from FFPE tissue was extracted and processed from 8 cases. DNA copy number alterations (CNA) and allelic imbalances (AI) were analyzed by genome-wide high-resolution SNP-array (OncoScan, Affymetrix).
Results: Our series include 18 patients [male=9, female=9] with a median age of 30 years (19-58) and a median follow up of 52 months (2 months - 19 years). Tumor morphologies were variable and included undifferentiated high grade/pleomorphic sarcoma (n=8), osteoblastic (n=5), chondroblastic (n=2), giant cell rich (n=1), telangiectatic (n=1) and sclerotic (n=1) sub types. Tumor sites included axial (n=7) and extremities (n=11). Five patients (28%) died of disease. Nine (50%) showed no evidence of disease while seven (39%) showed local recurrence and/or metastasis at last follow-up. Genomic analysis of oncogenes and tumor suppressor genes implicated in pediatric osteosarcoma showed frequent copy number alterations (gains and losses) in all 8 cases studied. Most common alterations included loss of heterozygosity, including deletion and copy neutral-LOH, of tumor suppressor genes *TP53* (50%), *CDKN2A* (63%), *RB1* (63%), *PTEN* (50%), *NF1* (50%) and *LSAMP* (63%). Homozygous deletion of *CDKN2A* was found in 25% of cases. In addition, amplifications or copy number gains of oncogenes were present as follows: *CDC5L, RUNX2* and *CCND3* at 6p.12-21 in 37% cases, MYC at 8q24 in 50% cases, *MDM2* and *CDK4* at 12q13-15 in 37% cases, *EGFR* in 25% cases.
Conclusions: 1) Our findings suggest that the primary adult skeletal osteosarcomas share many of the genetic alterations seen in pediatric osteosarcomas.
2) Follow-up showed 39% with local recurrence and/or metastatic disease and 28% died of disease.
3) Additional cases are being studied by SNP-array analysis and targeted next generation sequencing which may aid in the detection of genetic alterations that may be specific to primary adult skeletal osteosarcomas and thus may provide insight into their clinical behavior.

35 Histologic Spectrum of Giant Cell Tumor (GCT) of Bone in Patients < 18 Years of Age: A Study of 66 Patients

Alyaa Al-Ibraheemi, Jodi M Carter, Riyam T Zreik, Carrie Y Inwards, Karen Fritchie. Mayo Clinic, Rochester, MN; Scott & White Healthcare, Temple, TX.
Background: While the majority of GCTs occur in adult patients, occasionally they arise in the pediatric population. In this setting they may be mistaken for tumors more commonly seen in this age group, particularly osteosarcoma due to aggressive radiologic findings and the presence of immature bone. In order to better understand how to avoid this problem, we studied a series of GCTs in patients ≤18 years of age with an emphasis on the histologic features.
Design: All cases of primary GCT of bone in patients ≤18 years were retrieved from our institutional archives. H&E slides were examined with focus on: patterns of bone formation and fibrosis, mitotic activity, necrosis, atypia and collections of foamy histiocytes. Clinical records/radiologic data were reviewed in all cases.
Results: 66 (of 710) patients with histologically confirmed GCT of bone ≤ 18 years of age, including 45 females and 21 males (age range 8 to 18 years, median 16.5 years), were identified. Tumors involved the tibia (17), femur (14), sacrum (8), vertebral bodies (7), radius (5), humerus (4), metacarpal bone (3), fibula (2), and 1 each of the phalanyx, ulna, pelvis, patella, calcaneus and navicular bone. Of cases with available imaging, 24 were epiphyseal, 9 were metaphyseal, and 5 involved both. Mature bone was present in 19 tumors (29%); 36 tumors (54%) had irregular lace-like osteoid and 3 cases (4%) exhibited concentric whorls of osteoid. Zones of dense fibrosis, at times mimicking osteoid, were present in 28 of 66 cases (42%). The mitotic rate ranged from 1-35 mitoses/10 HPFs (median 5), necrosis was present in 12 tumors (18%), and 8 (12%) displayed collections of foamy histiocytes. None of the tumors showed cytologic anaplasia. Follow-up information (N=56, 6 to 840 months, median 83 months) showed 19 patients with local recurrence, and 1 with benign GCT lung metastasis. The median mitotic rates for those patients without recurrence, with recurrence and with metastasis were: 5 (range 1-35), 7 (range 1-24) and 7. 50% of tumors with necrosis recurred (6/12) compared to a recurrence rate of 11% (6/54) in tumors lacking necrosis.
Conclusions: GCT arising in the pediatric population is rare, representing 9% of GCTs seen at our institution. The morphologic spectrum of these tumors is broad and similar to that seen in patients >18 years of age. It is important to recognize patterns of osteoid deposition and fibrosis, seen in over 50% of tumors, and the common occurrence of mitotic activity in order to avoid a mistaken diagnosis of osteosarcoma, particularly on limited biopsy specimens.