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AUTOPSY

1 Cardiac Outflow Anomaly with large 5q31.3q32 microdeletion involving PURA and POU4F3

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Background: Purine-rich element binding protein A (PURA) encodes transcriptional activator protein Pur- and plays a significant role in neuronal development. 5q31.3 microdeletion syndrome, encompassing all or part of PURA has been reported in few individuals, with overlapping 5q31.2q31.3 microdeletion varying in size from 360 kb to 2.6 Mb and severe developmental delay. Here, we report a neonate with the largest (12.3 Mb) deletion extending from 5q31.3 to 5q32, involving both PURA and POU4F3 genes. POU4F3 gene, expressed in the sensory cells of the inner ear, is associated with progressive hearing impairment.

Design: Neonate with craniofacial abnormalities and congenital cardiac anomaly investigated with chromosome microarray

Results: A 1-day old male infant, born at 27 weeks estimated gestational age to a 19-year old mother, was identified to have a 5q31.3q32 microdeletion. The patient was prenatally diagnosed with congenital heart disease and was further found to have tetralogy of Fallot. This patient exhibited severe craniofacial abnormalities consistent with 5qmicrodeletion syndrome, including broad forehead, dolichocephaly, hypertelorism, long philtrum, and a tended upper vermillion. Further cranial abnormalities included absence of nasal bone, thickened nuchal fold, ventricular system dilatation with a lateral ventricle hematoma. The cardiac abnormality led to the patient's early expiration after 1 day.

Conclusions: This patient is first case in literature with cardiac anomaly and a 5q31.3 microdeletion, involving a large deletion (12.3 Mb) extending from 5q31.3 to 5q32. This case represents an early picture of a patient with 5q31.3 microdeletion syndrome involving both PURA and POU4F3 genes, and highlights the significance of investigating patients with early craniofacial abnormalities. Accompanying POU4F3 mutation was not previously reported in patients with 5q31.3 microdeletion syndrome. The role of POU4F3 in cardiac structure development is worth of further study.

2 Sensitivity and Specificity of Alzheimer Type II Astrocytes in Hepatic Encephalopathy

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Background: Hepatic encephalopathy (HE) is a neuropsychiatric disorder seen in patients with liver dysfunction in cirrhosis. Type II astrocytes are associated with hepatic encephalopathy. Very few studies have been done to correlate their presence in patients with hepatic encephalopathy.

Design: This is a retrospective cohort study in which cases and controls were included. Sections of basal ganglia were reviewed for the presence of type II astrocytes. Inclusion criteria for cases were those with cirrhosis or hepatic encephalopathy in clinical history. Medical records were reviewed for altered mental status and serum ammonia levels. Cases in which brain was not cut were excluded. Cases in which altered mental status was not present or ammonia levels were not elevated were included as controls. Criteria for identification of type II astrocytes included astrocyte enlargement (> 2 times size of oligodendroglial cells), chromatin margination, and 75% clearing of chromatin. The slides were read by principal investigator and sub-investigator utilizing the above criteria to minimize inter-observer variability. The cases and controls were blinded and read independently by both investigators. Total of 20 high power fields (HPF) were reviewed for cases and controls.

Results: Twenty-one patients with a diagnosis of HE were identified, with 35 patient controls (21 with altered mental status from various causes, 14 without altered mental status, 7 with hepatic insufficiency and 28 without hepatic insufficiency). Of the patients with a diagnosis of HE there was a mean of 19.8 type II astrocytes in 20 HPF (range 1 to 48). Patients with altered mental status without HE had an average of 6.7 type II astrocytes per HPF (range 0 to 43). Patients without altered mental status averaged 2.8 (range 0 to 12). Patients with hepatic insufficiency in the absence of HE averaged 17.4, ranging from 0 to 43, while patients with normal hepatic function averaged 6.5, ranging from 0 to 28. At a cut-off of 5 per 20 HPF, sensitivity for HE of 85.7% and specificity of 68.6%.

Conclusions: In the setting of altered mental status, Alzheimer type II astrocytes were present in all cases of HE. Nevertheless, they have modest sensitivity and specificity for HE, and these cells may be found in a wide range of conditions.

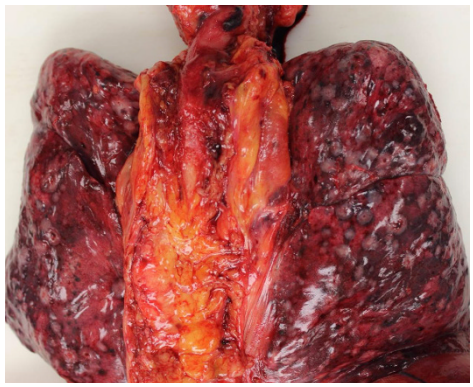
3 Glioblastoma With Extracranial Metastasis: Unique Findings At Autopsy

Karen R Arispe Angulo[1], *Frank Walch*[2], *Joy Tang*[3], *Arun K Singavi*[3], *Alexander Mackinnon*[4], *Jennifer Connelly*[3], *Elizabeth Cochran*[4]. [1]Medical College of Wisconsin, Wauwatosa, Wisconsin, [2]Medical College of Wisconsin, Milwaukee, WI, [3]Medical College of Wisconsin, [4]Medical College/WI, Milwaukee, WI

Background: Glioblastoma (GB) is the most common primary brain tumor in adults. Extracranial metastasis (ECM) is rare, occurring in < 2% of patients. This has been attributed to the blood-brain barrier, the absence of intracranial lymphatic channels, and the short survival of GB patients. Hypotheses of mechanisms of ECM are iatrogenic spread, direct extension into vessels, bone or around cranial nerves, and via intraventricular shunt placement.

Design: A 53-year-old male presented with headaches, left-sided weakness and personality changes. MRI brain scan showed a right temporo-parietal mass. Subtotal resection was obtained. Pathology showed GB, WHO grade IV, IDH1 wild type, ATRX retained, 1p19q non-codeleted, and MGMT unmethylated. He was treated with temozolomide and radiation followed by adjuvant temozolomide. Six months postoperatively he developed right temple soft tissue swelling; MRI showed a right periauricular soft tissue mass that was resected. Microscopic examination was consistent with metastatic GB to the parotid gland. One week later, he developed severe back pain; imaging demonstrated a T12 sclerotic lesion; biopsy showed GB. He was begun on bevacizumab and radiation to the T-spine and right periauricular area. CT spine, one week later, showed widely metastatic disease in multiple vertebrae, ribs, and sternum. He entered hospice care, and died 9.5 months after diagnosis; a complete autopsy was obtained.

Results: At autopsy, tumor deposits were found in the lungs (pleural & parenchymal, tan white nodules, 0.5-1.3 cm), liver (multiple hemorrhagic masses, 0.8-2.0 cm), and vertebral bone (irregular, tan white soft foci). Microscopic examination showed a neoplasm composed of spindle and epithelioid tumor cells, with necrosis, mitoses, and multifocal GFAP immunoreactivity, consistent with metastatic GB. Peribronchial lymph nodes and vascular invasion were evident. Molecular analyses on the primary and metastatic tumor tissue is in process.



Conclusions: In this case, the proximity of the original right temporo-parietal GB to the right parotid gland suggests seeding of the extracranial space with tumor cells. Once within the parotid gland, lymphatic channels were accessible. However, as most patients undergo craniotomy for GB but don't develop ECM, other factors are likely important. Molecular and genetic analyses of GB with ECM may aid in understanding of this rare development.

4 Metastatic Epithelial Tumors of the Adrenal Gland: A 26 Year Retrospective Autopsy Study

Jayjay Z Blanco[1], *Fatima Mir*[2], *Anam Naumaan*, *Prih Rohra*, *Waqas Mahmud*, *Pincas Bitterman*[1], *Vijaya Reddy*[1], *Paolo Gattuso*[3]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center, Chicago, Illinois, [3]Burr Ridge, IL

Background: Adrenal metastases are the most common malignant lesions involving the adrenal gland and the second most common tumor of the adrenal gland after benign adenomas. The common occurrence of metastases to the adrenal gland is related to its rich sinusoidal blood supply. We performed a retrospective analysis to determine the prevalence, types and origins of metastatic tumors involving the adrenal gland over a 26-year period.

Design: A retrospective study of autopsies performed on patients with history of malignant epithelial neoplasms was conducted (1992 to July 2017) and presence of metastases including the adrenal gland and extraadrenal gland were reviewed. The pertinent clinical and pathologic data were reviewed in detail.

Results: A total of 203 autopsies with history of epithelial malignancies were analyzed. 93 were males and 110 were females. Mean age of patients was 62 ranging from 15 to 93 years old. Lung was the primary site in 83/203 (41%) cases and breast was the primary in 27/203 (14%) cases. In the remaining cases, genitourinary tract (7.4%), liver (7%), pancreas (6.4%), colon (6%), prostate (3.5%), gynecological tract (3.5%), stomach (3%), esophagus (2.5%), larynx (2.5%), gallbladder (2%) and thyroid gland (1%) were the primaries. Metastases were present in 162/203 (80%) cases. Adrenal gland metastases were present in 49/162 (30%) cases. None of the cases showed isolated or solitary adrenal metastases. In 30/49 cases (61%), lung was the primary site while breast was the primary in 10/49 (20%) cases. In the remaining cases, genitourinary tract (8%), colon (4%), small bowel (2%), prostate (2%) and stomach (2%) were the primaries.

Conclusions: Adrenal metastases most commonly occurred in patients with lung, breast and genitourinary tract carcinomas. Adenocarcinoma was the most common histological subtype (77%) noted in the adrenal metastases from lung. Invasive ductal carcinoma was the most common histological subtype (70%) in adrenal metastases from breast primary. Isolated or solitary adrenal metastases are very rare and none of the cases in our study showed an isolated metastasis. A variety of tumors may give rise to adrenal metastases. They are often detected as a part of multiorgan metastases rather than isolated lesions of the adrenal gland. However, the incidence for any particular tumor may reflect the referral pattern of that institution.

5 Contribution of the Clinical Information to the Accuracy of the Minimally Invasive and the Complete Diagnostic Autopsy: a Study in sub-Saharan Africa

Paola Castillo[1], *Fabiola Fernandes*[2], *Llorenç Quintó*[3], *Miguel J Martínez*[4], *Juan Carlos Hurtado*[4], *Mamudo R Ismail*[5], *Lorena Marimon*[6], *Susan Jesri*[6], *Quique Bassat*[6], *Clara Menéndez*[6], *Carla Carrilho*[5], *Jaime Ordi*[7] [1]Hospital Clinic, Barcelona, [2]Hospital Central de Maputo, Maputo, [3]Institute for Global Health (ISGloblal), Barcelona, [4]Hospital Clinic, Universitat de Barcelona, Spain, [5]Maputo Central Hospital, Maputo, Mozambique, [6]Institute for Global Health (ISGloblal), [7], Barcelona

Background: High expectations have recently been placed in the validation of the minimally invasive autopsy (MIA), a technique based on the post-mortem sampling of key organs using needle biopsies. The MIA method was designed as a proxy, and eventually potential substitute, of the complete diagnostic autopsy (CDA), the gold standard methodology for cause of death investigation. The MIA has shown, when analyzed blindly to any clinical data, moderate to good concordance with the gold standard, the CDA enhanced with any available clinical data. We aimed to determine to which degree the use of clinical information improves the diagnostic precision of the MIA and, also, its contribution to the accuracy of the CDA, as opposed to the diagnoses obtained with the sole laboratory evaluation of the samples obtained through the postmortem procedure.

Design: Coupled MIA and CDA were performed to 264 cases (112 adults, 57 maternal deaths, 54 children and 41 neonates) at a tertiary hospital in Maputo, Mozambique. We compared the ICD-10 codes obtained by the MIA blind to clinical data (MIAb), the MIA enhanced with clinical information (MIAc), the CDA blind to clinical information (CDAb) with the results of the gold standard, namely the CDA enhanced with clinical data (CDAc). ICD-10 diagnostic codes belonging to the same chapter and block were considered as coincident. The concordance between the diagnostic categories obtained with the MIAb, the MIAc, and the CDAb with the gold standard was evaluated with the kappa coefficient, and the differences between the kappa values were assessed.

Results: The use of clinical data resulted in an improvement of the MIAb diagnosis (increase in diagnostic coincidence with the gold standard) in 30/264 (11%) cases. The clinical information was also critical to improve the CDAb diagnosis in 20/264 (8%) cases. The increase in concordance between MIAb and MIAc with the gold standard was particularly high in maternal (kappa value increasing from 0.485 to 0.836, $p<0.0001$), neonatal (kappa value increasing from 0.404, to 0.618, $p=0.0271$), and adult (kappa value increasing from 0.732, to 0.813, $p=0.0221$) deaths.

Conclusions: The use of clinical data improves significantly both the MIA and CDA diagnosis. The addition of clinical information may improve the results of the MIA diagnosis helping to provide more robust data for CoD surveillance in resource-limited settings.

Project funded by the Bill & Melinda Gates Foundation (Global Health grant numbers OPP1067522 and OPP1128001).

6 Correlation of Pre- and Post-Mortem Cardiac Findings in Heart Transplant Recipients

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Background: The clinical symptoms associated with cardiac rejection are nonspecific, and thus endomyocardial biopsy (EMB) remains the gold standard for diagnosis of rejection. However, EMB only samples a small portion of the right ventricle. This may reduce sensitivity for detection of cellular rejection, a process which may be spacially heterogeneous. We compared pre-mortem EMB results to cardiac findings at autopsy to assess the accuracy of pre-mortem diagnosis.

Design: The autopsy database was queried to identify cardiac allograft recipients who had undergone autopsy at our institution within the past 10 years. Clinical and pathologic data was obtained through medical record review.

Results: Autopsies were performed on 20 cardiac allograft recipients. Length of graft survival ranged from 20 days to 9041 days (average 2212 days). An average of 12.1 biopsies were performed on each patient. 10 patients underwent biopsy in the 30 days prior to death. One patient did not have sufficient biopsy material for evaluation. Seven biopsies were concordant for rejection. Two patients with 1R rejection (biopsies performed 22 and 27 days prior to death) did not have evidence of ACR at autopsy. Sensitivity for detection of ACR by EMB was 100% and specificity was 67%. For all five patients in which ACR was the primary cause of death, ACR was suspected clinically and/or confirmed by biopsy.

Conclusions: Although this study is limited by the small number of patients with pre-mortem biopsies, clinical impression and biopsy results appear to have good correlation with findings of ACR on autopsy.

7 The True Identity of a Widely Metastatic High Grade Neoplasm Revealed Only at Autopsy: A Case of "Dedifferentiated" Melanoma

Vincent Cracolici[1], *Shiraz Fida*[2], *Sabah Kadri*[3], *Mir Alikhan*[4], *Bekim Ameti*[5], *Jeremy Segal*[3], *John Hart*[6], *Thomas Krausz*[7]. [1]University of Chicago Medical Center, Chicago, IL, [2]University of Chicago Medicine, Chicago, IL, [3]University of Chicago, [4]Northshore University HealthSystem, Lincolnwood, IL, [5]University of Chicago Medical Center, [6]Univ. of Chicago, Chicago, IL, [7]The Univ. of Chicago Hosp, Chicago, IL

Background: Melanoma is known for its broad histomorphologic spectrum which, especially in the amelanotic forms, may be mistaken for a variety of other neoplasms. However, generally, immunohistochemical analysis leads to a firm diagnosis. Rarely, virtually all melanocytic markers can be negative (marker-negative melanoma).

Design: We present the autopsy findings of a 73-year old male with a history of an in-situ scalp melanoma with dermal features of regression. Three years following excision, he developed a mediastinal mass which on biopsy showed a high grade malignant neoplasm composed of dyscohesive, plasmacytoid/rhabdoid cells in a myxoid matrix. Apart from vimentin, this tumor did not express any of the tested lineage markers (S100, Melan-A, SOX 10, HMB 45, MiTF, cytokeratins, desmin, SMA, CD45) but had retained INI-1 expression. He died four days after admission.

Results: Autopsy revealed diffuse, soft, white masses in the mediastinum, right pleura, and peritoneum. Extensive sampling for histology showed a high-grade neoplasm with identical morphology and immunohistochemistry to the prior biopsy and, disappointingly, did not provide classification of the tumor. Grossly distinct from the majority of the tumor was a 1.5 cm nodule on the left pleura which was firm with a tan-brown, mottled cut surface.

Surprisingly, this nodule was biphenotypic: in addition to the plasmacytoid/rhabdoid cells, 50% exhibited a nested, vascularized pattern where many tumor cells contained melanin, making the diagnosis of metastatic melanoma apparent. Immunoreactivity for melanocytic markers (S100, HMB 45, Melan-A) supported this diagnosis and let us conclude that the immunonegative plasmacytoid/rhabdoid component was best regarded as "dedifferentiated" melanoma.

The intriguing finding of two phenotypically distinct yet adjacent melanoma morphotypes prompted next generation sequencing of the different components. This revealed identical polymorphisms in 63 genes, with nine unique mutations in the differentiated melanoma, and four unique mutations in the dedifferentiated melanoma (Table 1).

Table 1: Genetic Mutations Identified in Biphenotypic Melanoma Components

Mutations Present in Both Differentiated and "Dedifferentiated" Melanoma	Mutations Present only in Differentiated Melanoma	Mutations Present only in "Dedifferentiated" Melanoma
Sixty-three mutations including V600E BRAF and D100N TP63	R930X CTNNA E1317K XIRP 2 R461Q MAGI1 V1421F PKHD1 E78K GIMAP4 A55V RET G36R PTEN P637S ADAMTSL3 P191S SMAD2	R245C ROBO2 G2668Q DNAH5 R192W DEPTOR S41F LDLR

Conclusions: This case illustrates the value of autopsy in revealing the nature of malignancies and the importance of thorough gross examination. As a result, the prior diagnosis of an undifferentiated malignant neoplasm has changed to metastatic melanoma. Sequencing revealed many shared mutations in both tumor populations and four unique mutations in the dedifferentiated component which have not been described in melanoma.

8 Utility of Molecular Diagnostics to Solve a Diagnostic Challenge at Autopsy with Significant Ramifications for Family Members: Segmental Arterial Medialysis versus Vascular Type Ehlers-Danlos Syndrome

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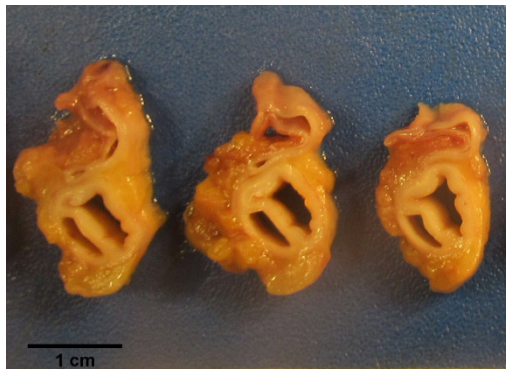
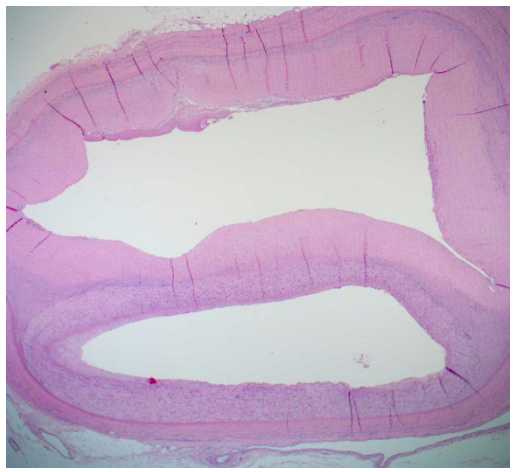
Background: Vascular Type Ehlers-Danlos Syndrome (EDS-IV) accounts for <4% of all EDS types. It is caused by a rare autosomal dominant COL3A1 gene mutation that predisposes to spontaneous vascular ruptures. Diagnostic criteria can prompt molecular screening in the clinical setting, but without such clinical data, the diagnosis of EDS-IV on autopsy is challenging. Vasculitis can be ruled out via histology; however, differentiating between histologically similar nonatherosclerotic, noninflammatory, arteriopathies, such as EDS-IV and segmental arterial medialysis (SAM), requires use of molecular diagnostics.

Design: We present an autopsy case of a 43-year-old man with a history of diabetes, cholecystectomy, and bilateral inguinal hernia repair. Of note, he had 10 children, one of which had died from an aneurysmal brain hemorrhage at an early age. He presented clinically with acute onset abdominal pain, diarrhea, emesis, and hypotension. Initial CT imagery demonstrated evidence of hemorrhage within the mesentery, retroperitoneum, and anterior mediastinum. CT angiography demonstrated aneurysmal changes of the aorta, celiac artery, and right external iliac artery; there was also a stable dissection of the left common iliac artery as well as a hemorrhagic dissection of the superior mesenteric artery (SMA). On hospital day six, the patient died, and an autopsy was requested to determine the cause of death.

Results: On autopsy, there was a transmural dissection of the SMA with extension of the hemorrhage into the retroperitoneum and pleural cavities. There were aneurysmal changes of the aorta, celiac artery, and right external iliac artery. Histologic examination of the left common iliac artery dissection did not reveal inflammatory cell infiltrate arguing against the diagnosis of vasculitis (see Figures). The unexpected findings included: bilateral hemothoraces, myocardial infarction, remote renal cortical infarcts, pulmonary emphysema, pulmonary osteometaplasia, and diffuse biliary hamartomas (von Meyenburg complex). Next generation DNA sequencing revealed a COL3A1 Exon 47 gene mutation consistent with a diagnosis of EDS-IV.





Conclusions: This case illustrates the difficulties associated with the post-mortem diagnosis of a spontaneous arterial rupture with limited clinical data. It highlights the role of next generation sequencing on autopsy to distinguish between two clinically similar vasculopathies, namely EDS-IV and SAM, which could potentially warrant genetic counseling for family members.

9 Pathological findings in placentas of 100 stillborns: A retrospective study

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Background: Disorders of placenta and umbilical cord are among the most important contributors to the risk of stillbirth during late pregnancy. The aim of the study was to evaluate spectrum and frequency of pathological findings in placentas of stillborns in second and third trimester of gravidity.

Design: 100 recent cases of placentas of stillborns of age ranging from 22 to 41 gestational weeks (mean 33.2 weeks) were retrieved from our archives and revised. Pathological findings were correlated with the results of fetal autopsy and maternal anamnestic data which were available in 84 cases.

Results: The most common pathological placental findings were maternal vascular lesions (24.1%), abnormal coiling or strangulation of the umbilical cord (19.1%), fetal stromal-vascular lesions (18.5%), placental inflammatory-immune processes (16.8%) and abnormal length of the umbilical cord (6.2%). In 56% of cases the pathological findings were considered to be the direct cause of intrauterine death. The mean maternal age was 31 years (range: 16 - 42 years). Maternal diseases were identified in 49 cases, the most frequent being thrombophilias (n = 26; 59.1%), which were clinically silent in 25 cases. Women in the series were mostly nulliparous (n = 36; 42.8%), but in 16 cases (19%) there was a history of one or more previous abortions. 8 women (50%) of these 16 cases were tested positive for at least one thrombophilia (mutations of genes *MTHFR*, *Factor V* (Leiden), *PAI-1*). Furthermore, in the placentas of mothers with thrombophilia the signs of maternal vascular malperfusion were found more frequently. Only in 3 placentas there were no pathological findings identified. Of those, in 2 cases maternal thrombophilia was present. Furthermore, one case was accompanied with HELLP syndrome, in another case the autopsy revealed prenatally unrecognized heart defect of the fetus. In the third case no additional information about mother was available.

Conclusions: Placental malfunction (especially due to maternal vascular lesions) in the second and third trimester may represent direct cause of intrauterine death in more than a half of cases. According to this study we also suggest that mothers with inherited thrombophilias are at increased risk of placental malfunction that may contribute to poor fetal outcome or even death, even though the thrombophilia is clinically silent. In some cases only the correct diagnosis of a placental disorder may indicate the necessity of medical intervention to prevent subsequent abortions.

10 Heart Retention Practices in a Forensic Pathology Unit

Linnea Duke[1], *Jacqueline Parai*[2], *Christopher Milroy*[3]. [1]Montreal, PQ, [2]University of Ottawa, [3]Ottawa Hospital, Ottawa, ON

Background: Medico-legal autopsies do not require consent and retention of organs may be required for diagnosis. Organ retention has ethical, legal and resource implications. In Ontario, the approximate medico-legal autopsy rate is 7% of all deaths. The Eastern Ontario Forensic Pathology Unit covers the City of Ottawa and surrounding counties. It also receives some cases from Nunavut and southern counties of Eastern Ontario (Kingston area). The main area served has a population of 1.2 million and the unit currently conducts 750 autopsies per year. This study analyzes specialist cardiac pathology referral in a forensic pathology unit. Literature on organ retention practices is limited and studies have primarily focused on neuropathology consultation.

Design: Autopsy reports detailing the referral of whole hearts for cardiac pathology opinion between July 2010 and December 2016 were reviewed. Data collected and categorized included (1) age of the deceased, (2) sex, (3) reason for consultation, (4) final cardiac diagnosis and (5) cause of death.

Results: 149 out of 4268 autopsies (3.5 %) met the inclusion criteria. In 116 of 149 (77.9%) cases, the post-mortem examination was performed because the death was sudden or unexpected. Of the 149 cases, 90 patients (60.4%) were male. The age range was zero days to 85 years, with a median age of 36 years. The principal reasons for cardiac consultation were for the evaluation of potential undiagnosed cardiac disease - 93 cases (62.4%), prior operative intervention - 34 cases (22.8%) and hearts with known congenital heart disease - 14 cases (9.4%). The final cause of death had a cardiac finding to account for death in 73 cases (49%), but in 27 cases (18.1%) the cause of death remained undetermined after cardiac pathology consultation. The final cause of death was attributed to cardiomyopathy in 19 of 149 (12.8%) cases, nine (6%) of which were attributed to arrhythmogenic cardiomyopathy and one to hypertrophic cardiomyopathy.

Conclusions: 3.5% of medico-legal autopsies had cardiac pathology consultation. In 49% of cases a cardiac cause of death was established by cardiac pathology analysis. However in 18.1% of cases, cardiac pathology was negative and the cause of death remained undetermined. Arrhythmogenic cardiomyopathy was found in 6% of referrals. In cases where the cause of death is attributed to an inherited cardiomyopathy or potential channelopathy, the practice identifies families that would benefit from a referral to a cardiologist or medical geneticist.

11 Consenting and Communications: The Twin Foundations of a Rapid Autopsy Program

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Background: Rapid autopsy for research provides a unique opportunity to sample tissue from multiple sites to elucidate the development of disease. As rapid autopsy is a relatively recent phenomenon, there are important lessons to learn about the process of informed consent and communication with next of kin and the effect of these steps on the Program.

Design: The Legacy Gift Rapid Autopsy program has operated in its current form since 2014 and has performed 48 cases across 10 organ systems. The program has a general IRB approved protocol which applies to research in all organ systems. Patients are initially referred to the Program by clinicians or hospice workers or are self-referred. Usually the patient signs a study consent which includes explicit permission for genetic testing, cell lines, tissue banking, and sharing of specimens with outside researchers. When the patient dies, the next of kin should immediately sign an autopsy consent (separate from a study consent) to allow the procedure to be performed. Our state requires autopsy consent to be signed after death by the legal next of kin, with no pre-mortem signing allowed. A flowchart will present the steps to be accomplished in the effective and appropriate consenting process for a Rapid Research Autopsy Program.

Results: 29 patients signed the premortem study consent, 8 parents signed for minor children, and 11 next of kin signed for incapacitated patients. The RAP Director frequently participates in open discussions about the process with families. In 2017 a 1-800 number was instituted for the convenience of families at the time of passing. Far from being an incidental detail, this shortened time from death to signing of the autopsy consent, as well as ensuring immediate contact. This has proven to be important in shortening the time from death to the rapid autopsy, thus contributing significantly to the usefulness of tissue recovered.

Conclusions: In the current legal climate, permission from patients themselves for sensitive testing such as growth of cell lines is crucial. Scrupulous attention to proper permissions and communication with families is essential to the continued use of postmortem specimens and the willingness of patients and their next of kin to participate in helping meet the best goals of rapid autopsies.

12 A Template for Successful Collaboration with Researchers in Rapid Autopsy Programs

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Background: A growing number of centers are interested in performing rapid autopsies (RA) to investigate the development of cancer and the efficacy of treatments. To accomplish this, it is necessary to fully plan an integrated procedure for maximum benefit. In rapid autopsy, time spent and not amount of tissue for collection is the limiting factor.

Design: Successful collaboration can be broken down for clinicians and researchers into a series of action steps:

THINK about how multi-site and parallel autopsy sampling might be used in your research

DEFINE your patient population, sample tissue and type, and postmortem interval needed

MEET with the RA Director or Coordinator to delineate interests, funding, and available staffing for cases

DISCUSS the Program with patients and their families

CONSENT of patients by researcher or arrange for RA Director to consent the study (if applicable)

COOPERATE to collect specimens at time of case and afterwards

COLLABORATE with RA pathologists on subsequent work

FEEDBACK to RA program about research results and define evolving needs

Results: The sequence of events in a successful prostate cancer case is reviewed. The study protocol was well delineated by the RA and prostatic researcher and the number of people required to complete the work was pre-planned (THINK, DEFINE, MEET). Premortem study consenting was performed by the Prostate Study Coordinator

(DISCUSS, CONSENT) and when the patient passed, the autopsy consent was completed and transport initiated (CONSENT). The autopsy was started at 0600 at a postmortem interval of approximately 7 hours. As well as the RA program staff, the prostate researcher and a team of three lab technicians participated. Fresh and frozen specimens were taken from 17 tumor sites, bone cores from 10 sites, and the prostate was entirely sampled (COOPERATE). An update meeting with the prostate researcher, RA Director and RA Fellow is planned and results of sequencing and immunohistochemical staining will be shared (COLLABORATE). FEEDBACK to follow.

Conclusions: Rapid autopsies are logistically complex but are able to provide large numbers of specimens from a wide variety of body sites. Because of the amount of tumor and numerous choices of sites to sample, advanced and collaborative planning between researchers and the autopsy pathologist is essential to success.

13 Development Of Pulmonary Arterial Hypertension After Liver Transplantation

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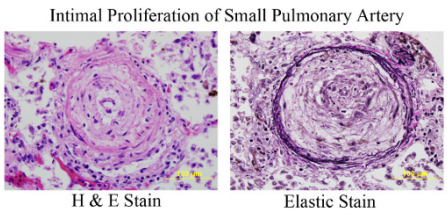
Background: Pulmonary arterial hypertension (PAH), defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15mm Hg and pulmonary vascular resistance (PVR) > 3 wood unit, is a rare complication of end stage liver disease and portal hypertension. This complication is referred to as portopulmonary hypertension (PPHTN). The main cause of PPHTN is speculated to be due to exposure of the pulmonary circulation to vaso-constrictive / proliferative mediators normally degraded by the liver. Therefore, liver transplantation is considered one of the mainstays of therapy for PPHTN, and resolution of PPHTN post liver transplantation is a well described outcome.

Design: Here we report a rare case of de novo development of PAH after liver transplantation. The patient was a 49-year-old female without previous history of PAH who underwent liver transplantation for Hepatitis C and alcohol-induced cirrhosis. Prior to transplantation she was diagnosed with hepatopulmonary syndrome by echocardiogram considered a complication of advanced liver disease. Five months after transplantation, she was diagnosed with severe PAH (mPAP = 65 mmHg, PVR > 11 wood units) and right heart failure. She was started on pulmonary arterial vasodilators including intravenous epoprostenol. Her PAH was refractory to aggressive vasodilator therapy and she died two weeks after diagnosis.

Results: At autopsy, she was found to have pleural and peritoneal effusions and right ventricular dilation and hypertrophy. Microscopic examination of lung, including elastic stains, showed that the small pulmonary arteries at the level of respiratory bronchioles had severe intimal proliferation and luminal obliteration without apparent medial hypertrophy. The more proximal pulmonary arteries had minimal intimal response with scant medial hypertrophy. Scattered plexiform lesion and multifocal pulmonary hemorrhages were also noted.



Conclusions: De novo PAH after liver transplantation is extremely uncommon and information on the underlying histopathology is limited. The unique pattern of segmental change of small pulmonary arteries hasn't been previously described. The presence of hepatopulmonary syndrome prior to liver transplantation could be a risk factor for the development of de novo PAH post liver transplantation. Our case in combination with others provides some histopathological insight into the de novo development of pulmonary vascular disease following liver transplantation.

14 Unkown Dihidropyrimidine Dehydrogenase Deficiency as a Cause of Fatal 5-Fluorouracil Toxicity

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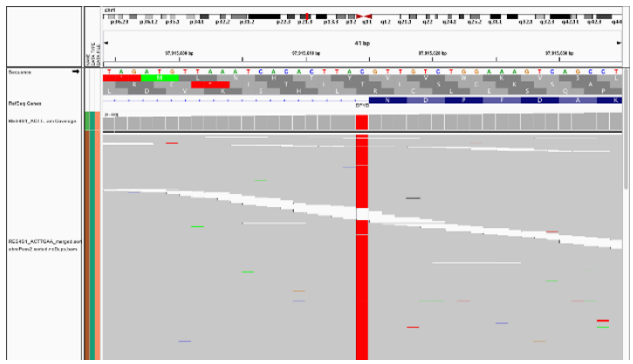
Background: 5-Fluorouracil (5-FU), in combination with other cytotoxic drugs, is commonly used to treat a variety of cancers. Dihydropyrimidine dehydrogenase (DPD) catalyzes the first catabolic step in 5-FU degradation, converting 80% of 5-FU to its inactive metabolite. Approximately 0.3% of the population demonstrate complete DPD deficiency, translating to extreme toxicity of 5-FU.

Design: We present the autopsy findings of a 54-year-old male with left base of tongue squamous cell carcinoma, admitted for first cycle of OPTIMA trial (dose reduced chemoradiotherapy) which included 5-FU, paclitaxel, and hydroxyurea. The clinical course was complicated by intractable diarrhea and refractory pancytopenia soon after initiation of therapy, both initially attributed to hydroxyurea. The patient subsequently developed sepsis, progressive desquamative lesions, acute kidney failure, and persistent hemodynamic instability, requiring intubation. Due to poor prognosis, he was transitioned to comfort care and expired.

Results: Autopsy revealed markedly hypocellular (<5%) bone marrow with diminished trilineage hematopoiesis and virtually no megakaryocytes, toxic epidermal necrolysis involving skin of head, chest, back and right arm, kidneys with diffuse acute tubular necrosis, and pale-appearing gastrointestinal tract with severely damaged mucosa. Post-mortem blood and bilateral lung cultures were positive for *Stenotrophomonas maltophilia*. Due to the precipitous clinical deterioration from chemotherapy and the described autopsy findings, DNA analysis by next generation sequencing was performed on normal liver tissue to evaluate for pathogenic *DPYD* variants, revealing a point mutation one base downstream of exon 14 (c.1905+1G>A) at approximately 100% variant allele frequency, consistent with homozygosity (Image 1).



Conclusions: The *DPYD* mutation identified in our case (designated *DPYD**2A, rs3918290) is the most common inherited polymorphism associated with 5-FU sensitivity, leading to impaired DPD protein product of the *DPYD* gene due to splicing error. Compound heterozygosity or homozygosity for deleterious *DPYD* alleles (as in our case) is associated with autosomal recessive DPD deficiency disorder which results in life-threatening toxicity following 5-FU administration, with an estimated 0.5% death rate. Cases like these suggest that expanded screening for *DPYD* mutation may be warranted to avoid morbidity and mortality from such a common chemotherapeutic drug.

15 Sessile Serrated Adenoma/Polyp of the Appendix: An Autopsy Study Addressing Frequency in the General Population

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Background: Sessile serrated adenoma/polyp (SSA/P) is the precursor of sporadic MSI-H colon cancer. A similar lesion has been described in the appendix, and some authors have suggested a link between appendiceal SSA/P and risk of subsequent colon cancer. The frequency of this lesion in the appendix is ill-defined, but a recent study found a surprisingly high rate (20%; n=11/55) in consecutive adult (>/= age 30) acute appendicitis cases in which the specimen was entirely submitted. The purpose of this study is to define the frequency of appendiceal SSA/P in the general adult population.

Design: At our institution, the appendix is routinely saved from autopsies including examination of the abdominal block (along with several other tissues in a stock bucket for a period of 18 months). Appendices from non-medical examiner cases were entirely submitted for histopathology as longitudinal sections through the tip and multiple transverse sections. The following were recorded: patient age, gender; number of sections; presence of SSA/P, fibrous obliteration, other significant pathology, or limiting autolysis. Mann-Whitney and Fisher's exact tests were used with p<0.05 considered significant.

Results: Eighty appendices (mean/median age 60; 42M:38W) were examined in an average of 19 sections. Three (3.8%) SSA/P were found (57, 74, 75 years; 3M; 3-5 sections involved). Patients with fibrous obliteration (61%; n=49) were significantly older (mean 63 vs. 54; p=0.013). Autolysis was somewhat limiting in 15. Other significant findings are listed in the Table.

Table: Findings in 80 Consecutive Adult Medical Autopsies

Finding	n (%)
Sessile serrated adenoma/polyp	3 (3.8%)
Incidental well-differentiated neuroendocrine tumor	3 (3.8%)
Incidental low-grade appendiceal mucinous neoplasm	2 (2.5%)
Endometriosis/endosalpingiosis	2 (2.5%)
Secondary involvement by cancer	2 (2.5%)
Melanosis appendicis	1 (1.3%)

Conclusions: SSA/P was found in 3.8% of consecutive, entirely submitted appendices from adult medical autopsies. This is significantly less frequent than in the recently reported acute appendicitis series (p=0.0034). Even if there is an association between SSA/P and a risk of subsequent colon cancer, this low rate of appendiceal SSA/P does not appear to justify entirely submitting the appendix in surgical cases. Its frequent occurrence in acute appendicitis suggests a role in the etiopathogenesis of that disease.

16 The Spectrum of Autopsy Neuropathologic Abnormalities in Non-ketotic Hyperglycinemia

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Background: Non-ketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is a genetic disorder of glycine metabolism. Most cases of NKH involve a mutation in the *GLDC* gene, which codes for glycine dehydrogenase. Affected infants present with hypotonia, feeding difficulties, intellectual disability and refractory seizures. Based on the severity of the presentations, the disease is classified into three major types: classical (neonatal) form, atypical form and transient neonatal hyperglycinemia. The neuropathology associated with NKH is not well studied, and some clinical symptoms, especially refractory seizures, cannot be explained by the previously described finding of vacuolating myelinopathy.

Design: Postmortem examination of the brain was performed on 5 cases of NKH (male:female = 2:3), including three cases of confirmed *GLDC* mutations. There were 3 classic forms and 2 atypical forms. Cases of classic forms presented with symptoms at birth and died within 3 months. One case of atypical form had neonatal onset, and the other had insufficient clinical information. Patients with atypical form survived for 7 and 48 years, respectively.

Results: Clinical presentations of all classical form and one atypical form cases were similar, including lethargy, hypotonia and seizures. The atypical form case had a better developmental outcome. The gross examination of the brains, in comparison, demonstrated a wide spectrum of findings ranging from unremarkable brain, cortical atrophy to multicystic encephalopathy. Further examination of histology also revealed a range of abnormalities, including vacuolating myelinopathy (3 of 5 cases), cortical neuropil vacuolation (2 of 5 cases), laminar necrosis, balloon neurons, neuronal heterotopia and type 1A focal cortical dysplasia (FCD).

Conclusions: The neuropathologic abnormalities of NKH, even within the classical form, are highly variable and not restricted to vacuolating myelinopathy as previously reported. The findings of neuronal heterotopia, balloon neurons and FCD indicate that seizure in NKH is not solely caused by white matter abnormalities. They also suggest a possible role of *GLDC* mutations/variants in childhood epilepsy.

17 Impact of an Office of Decedent Affairs on Hospital Autopsy Rates, Autopsy-Related Communication, and Decedent Family Experiences

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Background: Despite clear clinical and academic utility, the hospital autopsy has become increasingly less common over the past 50 years. While removal of minimum autopsy rate standards by JAHCO in the 1960s is believed to be a major driver, we hypothesized that a lack of direct communication between pathology, the clinical team, and the decedent's family is also a contributor. As part of an institutional initiative, a pathology-run Office of Decedent Affairs (ODA) was launched to guide decedent families after an inpatient death including bereavement counseling, organ donation, and autopsy. We hypothesized that the ODA would increase hospital autopsy consent rates while improving communication and decedent family experiences.

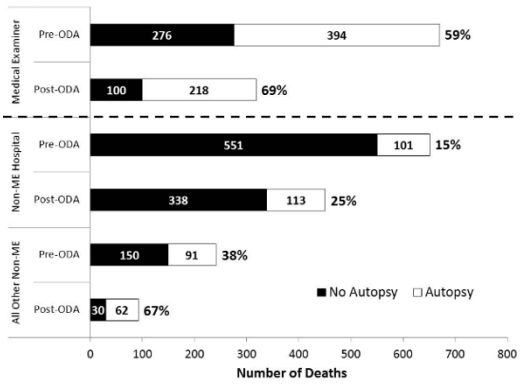
Design: Pre-ODA and post-ODA cohorts were defined as all non-medical examiner (non-ME) inpatient deaths at Mayo Clinic (Rochester, MN) from 6/1/2013 through 5/31/2014 and 7/1/2016 through 12/31/2016 respectively. Electronic medical records were abstracted for demographic data, death information, documented autopsy-related communication, and autopsy findings. Comparative statistical analyses were performed using the student's t-test and ^{2} test. Telephone interviews were completed with four next-of-kin groups (pre-ODA vs post-ODA; consented vs refused) on their experiences and decisions regarding autopsy.

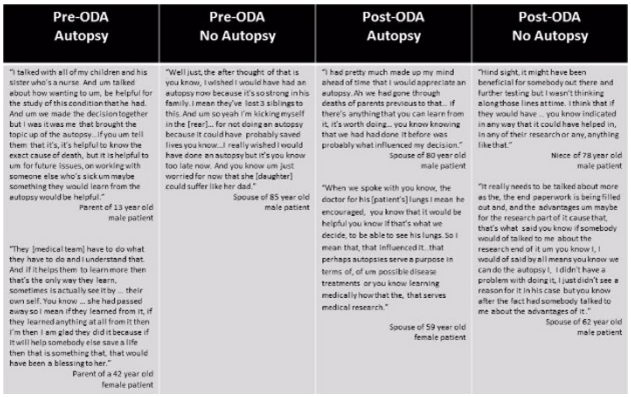
Results: There were 652 pre-ODA and 451 post-ODA deaths with 15% and 25% autopsy consent rates respectively ($p < 0.001$; Figure 1) without any significant differences in age, sex, or time of death (Table). There were significant increases in both family discussions about autopsy and bereavement counseling. For those consented to an autopsy, there were significant increases in final autopsy result communication rates and higher rates of unexpected autopsy findings. More NOK in the post-ODA interview groups recounted autopsy-related discussions with the healthcare team than those in the pre-ODA interview groups (Figure 2). For those who consented, multiple decedent conditions and altruism (pre-ODA) or autopsy knowledge/prior experiences and medical team recommendations (post-ODA) were influential factors. Most NOK who refused autopsy stated that an explanation about the role of autopsy in research could have influenced their decision.

Pre-ODA and post-ODA demographic and autopsy-related communication data

*8 subjects excluded from electronic medical record audit (high security patients)

	All Non-ME Hospital Deaths			Autopsy Cases Only		
	Pre-ODA	Post-ODA	p-value	Pre-ODA	Post-ODA	p-value
Number*	645	450	--	97	112	--
Age in years (mean ± SD)	65.3 ± 22.6	65.2 ± 22.9	0.92	59.8 ± 24.9	64.2 ± 21.1	0.17
Female (%)	275 (43%)	198 (44%)	0.65	44 (45%)	43 (38%)	0.31
Date/Time of Death (%)	--	--	1.0	--	--	0.91
Weekday Working Hours	203 (32%)	141 (31%)		34 (35%)	41 (37%)	
Weekday After Hours	245 (38%)	172 (38%)		34 (35%)	36 (32%)	
Weekend	197 (30%)	137 (31%)		29 (30%)	35 (31%)	
Patient asked about autopsy (%)	41 (6%)	23 (5%)	0.39	--	--	--
Family asked about autopsy (%)	570 (88%)	445 (99%)	<0.001	--	--	--
Bereavement counseling provided (%)	313 (49%)	440 (98%)	<0.001	--	--	--
Unexpected autopsy findings	--	--	--	45 (46%)	67 (66%)	0.05
Final autopsy report/ findings to family	--	--	--	38 (39%)	95 (85%)	<0.001





Pre-ODA Autopsy	Pre-ODA No Autopsy	Post-ODA Autopsy	Post-ODA No Autopsy
"I talked with all of my children and his sister who's a nurse. And um talked about how wanting to um, be helpful for the study of this condition that he had. And um we made the decision together but I was it was me that brought the topic up of the autopsy. If you um tell them that it's, it's helpful to know the exact cause of death, but it is helpful to um for future issues, on working with someone else who's sick um maybe something they would learn from the autopsy would be helpful." Parent of 13 year old male patient "They [medical team] have to do what they have to do and I understand that. And if it helps them to learn more then that's the only way they learn, sometimes is actually see it by ... their own self. You know ... she had passed away so I mean if they learned from it, if they learned anything at all from it then I'm then I am glad they did it because if it will help somebody else save a life then that is something that, that would have been a blessing to her." Parent of a 42 year old female patient	"Well just, the after thought of that is you know, I wished I would have had an autopsy now because it's so strong in his family. I mean they've lost 3 siblings to this. And um so yeah I'm kicking myself in the [rear]... for not doing an autopsy because it could have probably saved lives you know...I really wished I would have done an autopsy but it's you know too late now. And you know um just worried for now that she [daughter] could suffer like her dad." Spouse of 85 year old male patient	"I had pretty much made up my mind ahead of time that I would appreciate an autopsy. Ah we had gone through deaths of parents previous to that... if there's anything that you can learn from it, it's worth doing... you know knowing that we had had done it before was probably what influenced my decision." Spouse of 80 year old male patient "When we spoke with you know, the doctor for his [patient's] lungs I mean he encouraged, you know that it would be helpful you know if that's what we decide, to be able to see his lungs. So I mean that, that influenced it, that perhaps autopsies serve a purpose in terms of, of um possible disease treatments or you know learning medically how that the, that serves medical research." Spouse of 59 year old female patient	"Hind sight, it might have been beneficial for somebody out there and further testing but I wasn't thinking along those lines at time. I think that if they would have ... you know indicated in any way that it could have helped in, in any of their research or any, anything like that." Niece of 78 year old male patient "It really needs to be talked about more as the, the end paperwork is being filled out and, and the advantages um maybe for the research part of it cause that, that's what said you know if somebody would of talked to me about the research end of it um you know I, I would of said by all means you know we can do the autopsy I, I didn't have a problem with doing it, I just didn't see a reason for it in his case but you know after the fact had somebody talked to me about the advantages of it." Spouse of 62 year old male patient

Conclusions: A pathology-run ODA significantly increased hospital autopsy rates, documented autopsy-related communication with family, and family bereavement counseling. The ODA also altered the factors that influenced NOK to consent to an autopsy.

18 The Lethal Twist – A Story of Unspoken Pain: Small Intestinal Volvulus, a Fatal Complication Involving an Infrequent site in a Patient with Cerebral Palsy

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Background: Small intestinal volvulus is the abnormal twisting of bowel around the axis of its mesentery, leading to obstruction and vascular compromise, resulting in bowel ischemia and necrosis which are life threatening. Risk factors include malformations, malrotations and adhesions. This rare occurrence presents with nonspecific symptoms of abdominal pain, nausea and vomiting. Conventional radiographs fail to establish small intestinal volvulus as the cause of the obstruction. Its infrequent incidence and vague clinical presentation make it a difficult diagnosis. Delay in surgical intervention can be rapidly fatal.

Studies suggest increased frequency of intestinal obstruction in cerebral palsy patients. Cases of gastric and cecal volvulus have been reported in these patients especially in conjunction with kyphoscoliosis. There are no reported cases of small intestinal obstruction in association with cerebral palsy.

Design: We present a case of a 21-year-old man with severe cerebral palsy and kyphoscoliosis, who was being fed through a PEG tube for the past several years. The patient presented to the emergency room with respiratory distress and abdominal distension. A surgical abdomen was noted. Abdominal X-rays revealed gas patterns suggestive of small intestinal obstruction. The patient rapidly deteriorated and resuscitation attempts were unsuccessful.

Results: Autopsy revealed peritoneal cavity filled with extensively dilated and thin-walled loops of small intestine. Twisting of the small intestine, showing 360° rotation around the mesenteric root in a clockwise manner at two separate sites, was noted. The mesenteric veins were engorged. On bowel dissection, mucosal folds were absent and mucosa was green with patchy areas of hemorrhage consistent wth ischaemic necrosis. There was no evidence of any malformations, malrotations or adhesions.

Histopathological examination of the dilated segments revealed focal transmural hemorrhage with diffuse thinning of epithelium and muscularis propria.

Conclusions: Small intestinal volvulus is a rare entity with nonspecific clinical presentation that poses a diagnostic challenge. This autopsy highlights the need to maintain a high index of suspicion for small intestinal volvulus in cases of bowel obstruction in cerebral palsy patients to expedite surgery and prevent mortality. The primary care giver, in these cases, should be educated to recognize early signs of intestinal obstruction as potential volvulus and seek emergent care preventing treatment delays.

19 Benign Lymph Node Microenvironment is Associated with Response to Immunotherapy

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Background: Bystander benign lymph nodes in cancer patients have been considered hubs of immune surveillance against tumor. The microenvironment of these lymphoid tissues can be immune suppressed, hence allowing for tumor progression. Novel therapies with immune checkpoint inhibitors may help abrogate the suppression and recruit cytotoxic T cells to sites of disease. We hypothesize that patients who fail to respond to immunotherapy would show retained and proliferative cytotoxic CD8+ T cells in uninvolved lymph nodes with a compensatory increase in macrophages.

Design: Benign lymph nodes and spleen were evaluated from a total of 8 patients treated with immunotherapy that had subsequent postmortem examination. We used the AQUA method of quantitative immunofluorescence (QIF) to assess tumor infiltrating lymphocyte and macrophage protein expression and to characterize T-cell subsets by their activation status using a novel multiplexed QIF assay including CD3, Granzyme B and Ki67.

In addition, we performed traditional immunohistochemistry to qualitatively correlate the results of QIF. The above assessments were performed independently and in parallel, with all investigators blinded to clinical outcome during data collection.

Results: Benign lymph nodes from non-responders to immunotherapy (n=2) show significantly higher expression of cytotoxic markers like Granzyme B as well as significantly higher proliferation index (Ki-67) in T cells compared to responders (n=6). Higher expression of CD68 and PD-L1 in macrophages was also observed. While there was no significant difference in CD3 expression, higher levels of CD8+ T cells as well as CD20+ B cells was seen in the lymph nodes of non-responders. Aside from slightly higher granzyme B expression in the spleen of non-responders, no significant differences were seen between responder and non-responder splenic tissue. These findings were supported by traditional immunostaining methods.

Conclusions: While most studies in predictive biomarkers for immunotherapy focus on the tumor microenvironment, we show that benign lymph node microenvironment may be associated with response to immunotherapy. In responding patients, bystander lymph nodes appear to have been mobilized, resulting in reduced numbers of cytotoxic T cells. Conversely, patients whose disease progressed on immunotherapy appear to demonstrate higher levels of immune cells such as macrophages that express increased PD-L1, and activated T-cells that have not been recruited to the tumor site.

20 Tumor Heterogeneity can be Assessed by Exome Sequencing of Cell-free DNA in Post-mortem Blood Sample: The "Liquid Autopsy"

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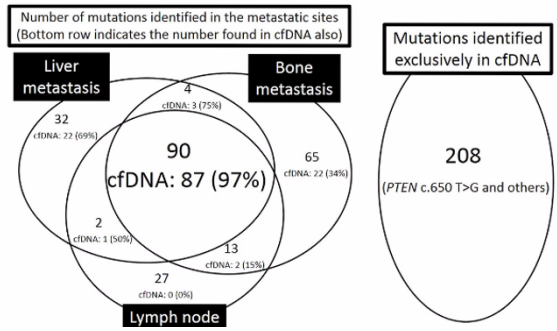
Background: Rapid autopsy has provided considerable insight into the progression and heterogeneity of cancer. However, it is not always feasible to sample all tumor sites, and performing exome or transcriptome analyses on numerous cancer samples is costly. Recent studies have shown that genomic profiling of plasma cell-free DNA (cfDNA) facilitates determination of the mutational status of cancer. In this study, we assessed the association between post-mortem plasma cfDNA and the mutational status and heterogeneity of cancer.

Design: We performed a rapid autopsy on a patient who died of advanced prostatic cancer (ERG-negative). Metastatic lesions in the liver, bone, and lymph nodes were sampled and snap-frozen. In addition, blood was drawn from the inferior vena cava. Pathological diagnosis of the case was made using routinely sectioned formalin-fixed paraffin embedded (FFPE) tissue, which included more than 50 metastases. The DNA extracted from frozen samples of liver, bone, and lymph node metastases, and cfDNA extracted from post-mortem plasma, were subjected to exome sequencing. Among the mutations present exclusively in cfDNA, we further investigated the *PTEN* mutation. The region containing the *PTEN* mutation was Sanger-sequenced using DNA extracted from a large number of FFPE cancer samples (15 liver, 14 lymph node, and 2 lung metastases).

Results: By exome sequencing, 233 mutations and 345 mutations were detected in metastatic lesions and cfDNA, respectively. Of the 90 clonal mutations which were commonly detected in the liver, bone, and lymph node metastases, 87 (97%) were found in cfDNA (Figure 1). In total, 208 mutations, including a *PTEN* mutation (c. 650T>G), were found exclusively in cfDNA. Sanger sequencing of the *PTEN* in 31 FFPE metastatic lesions revealed a mutation in 1 of 15 liver metastases, 1 of 14 lymph node metastases, and 1 of 2 lung metastases (Table).

	PTEN (c. 650T>G) mutational status
Liver metastasis 1	Wild type
Liver metastasis 2	Wild type
Liver metastasis 3	Wild type
Liver metastasis 4	Wild type
Liver metastasis 5	Wild type
Liver metastasis 6	Wild type
Liver metastasis 7	Wild type
Liver metastasis 8	Wild type
Liver metastasis 9	Wild type
Liver metastasis 10	Wild type
Liver metastasis 11	Wild type
Liver metastasis 12	Wild type
Liver metastasis 13	Wild type
Liver metastasis 14	Mutant
Liver metastasis 15	Wild type
Lymph node 1 (cervical)	Wild type
Lymph node 2 (paraaortic)	Mutant
Lymph node 3 (paraaortic)	Wild type
Lymph node 4 (paraaortic)	Wild type
Lymph node 5 (paraaortic)	Wild type
Lymph node 6 (paraaortic)	Wild type
Lymph node 7 (peripancreatic)	Wild type
Lymph node 8 (peripancreatic)	Wild type
Lymph node 9 (peripancreatic)	Wild type
Lymph node 10 (peripancreatic)	Wild type
Lymph node 11 (peripancreatic)	Wild type
Lymph node 12 (peripancreatic)	Wild type
Lymph node 13 (Right hilar)	Wild type
Lymph node 14 (Right hilar)	Wild type
Lung metastasis 1	Wild type
Lung metastasis 2	Mutant



Conclusions: Exome sequencing of the cfDNA in post-mortem blood enabled identification of the majority of clonal mutations. Furthermore, we detected mutations that would not have been detected by multiple frozen tissue sampling. Our results show that cfDNA reflects tumor heterogeneity. Therefore, we postulate the novel and cost-effective concept of "liquid autopsy", which involves two steps: exome sequencing of cfDNA followed by Sanger sequencing of relevant genes in FFPE samples.

21 A Review of the 'July Effect' and Autopsy Statistics in Three Teaching Hospitals in New York City

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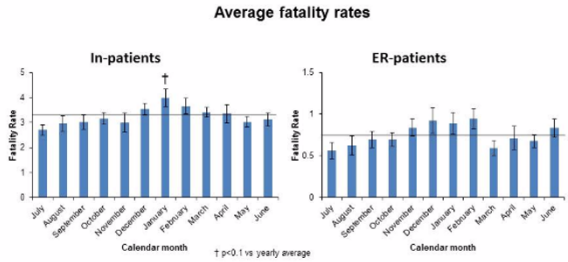
Background: The ' July Effect' is where hospital deaths are reported to be higher during July. The accepted notion is that new resident physicians begin with the expected knowledge and skills gap leading to increased medical errors, morbidity and mortality. Previous work is ambivalent on this data, thus, we set out to compare the hospital deaths to inpatient admissions, throughout the year in three urban hospitals to determine if there are any adverse outcomes associated with the start of the academic year.

Design: We performed a retrospective study to include the data for three teaching hospitals within our system, the number of monthly autopsies and in-hospital deaths and compared this to the number of monthly hospital admissions over the last four academic years, in this way we established the fatality rate, the autopsy rate and based on the yearly average for each hospital singly and as a group. The number of autopsies was determined using the electronic medical system, while the number of deaths and admissions was obtained from hospital statistics. The ratios of mortalities to autopsies and mortalities to admissions were compared for July to the other months and to the monthly average to determine if there was a statistically significant increase in autopsies or deaths in the month of July.

Results: The number of autopsies fluctuated yearly but July had no significant increase comparing to other months or in relation to the yearly average. Autopsy number also showed no correlation to the number of deaths in all sites. There was a significant increase in hospital deaths in January and February in comparison to both the yearly average and July which had the lowest. The mortality rate similarly showed a significant increase during January and February in one site and January only in another with the last site showing no change, all three sites showed a decrease in in-hospital deaths during July comparing to the yearly average. The emergency department death rate showed a similar pattern with an increase in January and a decrease in July. There is no significant decrease in the autopsy rate over the four academic years.



Conclusions: There is no correlation between autopsy number and mortality rate and January and February have the highest fatality rate. Even though it is commonly believed that July is most dangerous to be a hospital patient, here we show results opposite to the established perception. We also show there is no significant decrease in the number of autopsies over the last four years

22 Lactobacillus Septicemia Secondary to Aspiration Pneumonia in the Setting of Probiotic Use and Gastric Outlet Obstruction

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Background: Probiotics are medicinal products and/or food-stuffs which contain organisms thought to be beneficial to human health by modulating the normal microbiota. Typically, probiotics are delivered in capsule form, and contain a multitude of different bacterial and yeast genera, including *Lactobacillus* and *Saccharomyces*. The exact composition of organisms present varies from manufacturer to manufacturer. Sepsis secondary to probiotic use is a rare phenomenon, but has been previously reported in associated with immunosuppression or perturbations to the mucosal barrier of the gastrointestinal tract. Here we report the findings at autopsy for a patient who had consumed probiotics and subsequently aspirated the probiotic material, leading ultimately to *Lactobacillus* septicemia and death.

Design: We performed a complete autopsy on a 65-year-old male with stage IV gastric cancer, who presented to a regularly scheduled clinic appointment with fever, chills, and hypotension. The patient was referred to the emergency room with concerns of sepsis, and immediately upon arrival lost consciousness and experienced pulseless electrical activity, refractory to multiple resuscitation attempts.

Results: At autopsy, an NG tube placed because of copious amounts of vomitus during resuscitation was found to be occluded by several rubbery medicinal capsules. Within the stomach, approximately 15 medicinal capsules were identified in varying stages of digestion. These capsules histologically exhibited a multitude of bacterial organisms and yeast forms. Additionally, there was evidence of organizing pneumonia in the bilateral lungs, with capsule fragments identified in the terminal airways, and a robust acute inflammatory response. Multiple yeast forms were identified in these sections by GMS staining, and lung cultures were positive for *Lactobacillus* and more than four species of anaerobic gram-positive organisms. These results matched the patient's premortem blood cultures. Post-mortem lung cultures were also positive for *Candida glabrata* and *Candida albicans*, two species of yeast frequently isolated from the gastrointestinal tract, further supporting the hypothesis of gastric aspiration.

Conclusions: Sepsis secondary to probiotic use is a rare phenomenon, but should be considered in the appropriate clinical context. In the case of our patient, the almost-complete gastric obstruction and chemotherapy-associated immunosuppression likely led to an increased propensity for infection secondary to aspiration.

23 Print-culture as a Method of Microbiological Assessment: A Case Series and Comparison to Standard Culture Techniques

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Background: Diagnosis of infections often requires culturing of the microorganism, which can be challenging in the case of anatomic pathology specimens. Processing of surgical specimens has the potential to limit recovery of infectious agents from tissue, and most gross pathology suites are considered contaminated spaces where proper aseptic technique can be challenging. Print-culture is a method in which a frozen section of potentially infected tissue is performed and the section is placed on microbial growth media in an attempt to recover microorganisms present within the tissue. While the technique has been described for use in the autopsy setting, a formal comparison to modern culture techniques, and feasibility for use in the setting of surgical pathology setting, has yet to be performed.

Design: Print-culture was performed on 11 potentially infected sites in a series of autopsies without use of aseptic technique, and the results were compared to standard culture methods. A standard frozen section was performed on each specimen, and a 20um section of tissue was placed on growth media. The plates were evaluated daily for growth within the tissue compartment and the OCT compartment of the plated section. The results of an initial biochemical evaluation of the colonies present were compared to standard culture results. H&E staining of serial sections was also performed for histopathologic correlation.

Results: Print-culture was able to recover organisms in all cases suspicious for infection, including fungal infections. Colonies were considered true infections when organisms were present within the tissue compartment. Two sections containing true infections showed similar colonies outside of the tissue section, representing transfer of infectious agents from the tissue compartment into the OCT compartment. Sections demonstrating growth only within the OCT compartment were considered indicative of contamination. Interpretation of the microbial growth patterns was supported by histopathologic correlation in all cases, and standard microbiology results tended to correlate with the print-culture results.

Conclusions: Overall, print-culture was able to rapidly detect the predominant organisms present in an infectious nidus, while also providing rapid histologic evidence of active infection. Conceptually, this protocol could also be utilized in surgical specimens, including those sent for intraoperative consultation.

24 Discrepancies Between the Clinical and Anatomic Cause of Death Detected by Autopsy; a Barnes-Jewish Experience.

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Background: The autopsy has historically been an essential medical tool, and up until recently, a common hospital practice. From the early 1970s to recently, hospital autopsy rates in the U.S. have declined significantly; however its value as a quality assurance tool to reveal undiagnosed pathologies has been shown repeatedly. Previous studies have shown discrepancies between the clinical and anatomic cause of death to have a median overall rate of 23.5% including 9% for major discrepancies. Here we show the experience at Barnes-Jewish Hospital, a large tertiary care center, to be similar.

Design: A retrospective chart review of the autopsy records at Barnes-Jewish Hospital from 2013-2016 was completed. Only complete autopsies of adults with a hospital stay of greater than 24 hours were included. A total of 536 cases were reviewed for discrepancies between the clinical and anatomic causes of death and subsequently classified using the Goldman criteria, with a focus on classes 1 and 2. The discrepancies were then subclassified based on the disease process. The discrepancies were verified by secondary review of the decedent's electronic medical record.

Results: Of the 536 cases that met inclusion criteria, 14.4% (77) cases were found to have discrepancies that met either Goldman class 1 or 2 criteria. Class 1 and 2 discrepancies were identified at a rate of 6.4% (34) and 8.0% (43) of total reviewed cases. Subclassification of discrepancies based on disease process showed the following frequencies: Cardiovascular/Vascular (35, 45.5%), Infectious (24, 31.2%), Neoplastic (11, 14.3%), CNS related (3, 3.9%), and "Other" (4, 5.2%).

Conclusions: Despite the dramatic drop in hospital based autopsies, it continues to be an effective quality assurance tool. The above data show that a significant number of clinically relevant pathologies go undiagnosed at the time of death, and that despite decreasing frequency in many hospitals, the practice of routine autopsy should remain a hospital priority.

25 Etiology of Third Trimester Stillbirth

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Background: 40-75% of cases of fetal demise are considered unexplained in the obstetrical literature. Cord entanglement, placental insufficiency, maternal conditions, and fetal anomalies have all been implicated in fetal death. There are few published relevant data in the pediatric and perinatal pathology literature. We seek to establish that most late fetal deaths are explicable based upon a combination of fetal autopsy, placental examination, and clinical information.

Design: All autopsies performed on stillborn third trimester (> 28 weeks' gestation) fetuses from January 1998 to September 2017 were reviewed. Cases without placental examination were excluded. In the 179 cases fetal death was attributed to one or more categories: placental abnormalities, umbilical cord compromise, infection, fetal abnormalities, and unexplained.

Results: A cause of fetal death was determined in 157/179 (89%) of cases (142/162 (87.7%) of macerated fetuses and 17/17 (100%) of fresh stillbirths). 93/179 cases (52%) were attributed to umbilical cord compromise; 19/179 (10.6%) to intrinsic placental pathology; 35/179 (19.6%) to placental malperfusion (of these, there was an underlying maternal disorder in 13); 12/179 (6.7%) to fetoplacental infection; and 5/179 (2.8%) to fetomaternal hemorrhage. Only 1 fetal death (0.6%) was attributable to a fetal abnormality. 20/179 (11%) of cases remained unexplained. Of 26 cases with contributory maternal conditions such as pre-eclampsia 17 (35%) had concordant placental findings.

Conclusions:

1. Successful determination of the cause of fetal demise, which depends upon integration of findings from fetal autopsy, placental examination, and clinical information such as circumstances of the delivery (eg, placental abruption and cord entanglement), may reach nearly 90%.

2. The most common condition associated with fetal demise is umbilical cord compromise.

3. With rare exceptions fetal anomalies do not contribute to *in utero* demise.

4. In the absence of placental pathology maternal conditions such as advanced age and hypertension are not adequate explanations for fetal death, but should always be included in clinical history provided to the pathologist.

5. Fetal maceration does not preclude successful identification of the cause of fetal demise.

26 Consolidation: Pneumonia and Other Pathologies on the Bellevue Hospital Autopsy Service in 1897, the Year the Five Boroughs Became New York

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Background: On January 1, 1898, New York City consolidated the five boroughs to create the modern municipal government. This legislation reorganized the borough-based coroner system and death recordkeeping. The previous year, the world-renowned Bellevue Hospital Medical College pathology department lost its morgue in a fire. Among the records saved in the aftermath, recently rediscovered, were log books documenting hundreds of autopsies performed at Bellevue Hospital in 1897.

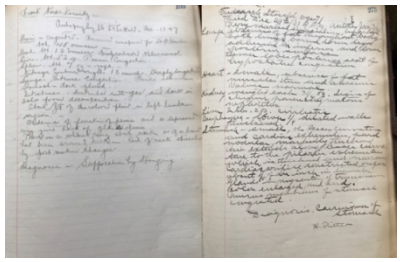
Design: Data from 324 autopsies (n=325, excluding one duplicate entry) performed at Bellevue Hospital between March 16 and December 31, 1897 were collected in a Microsoft Excel 2010 spreadsheet. Each decedent's name, age, race, ethnicity, country of origin, medical division, ward assignment, time of death, time of autopsy, and autopsist(s) were recorded, along with external examination findings, gross findings by organ system, and final anatomic diagnosis. Frequency tables and measures of central tendency were compiled. The final anatomic diagnoses were subcategorized by etiology (chronic disease, malignancy, infectious disease, therapeutic complication, medicolegal, psychiatric). Where possible, patient and physician identifiers were matched to contemporaneous public records, medical journals, and online archives (NYU Health Sciences Library, New York Public Library, National Library of Medicine). Microscope slides and laboratory medicine results were unavailable.

Results: Decedents included 222 men, 82 women, and 20 of unknown sex. Age was recorded for 166 adults and 46 children. The adults' average age at death was 42 years (range 19-78 years); children, 17 months (3 days-13 years). The majority (310) were U.S. born, with 11 European-born (Ireland, Germany, Austria, Italy, Sweden), 3 of unknown birthplace. Six U.S.-born were identified as "colored." The combined medical divisions ordered 208 autopsies, and the surgical 21. Other decedents were from the insane pavilion (2), emergency ward (1), prison (1), and found on the street (6). Average turnaround time was 43 hours (1 hour-14 days after death). Thirty-nine autopsies were same-day.

Final Diagnosis (Chronic and Infectious)	Frequency
Tuberculosis (pulmonary and miliary)	116
Nephritis (Bright's disease)	88
Pneumonia	69
Meningitis	31
Cardiovascular disease	30
Cirrhosis of the liver	14
Peritonitis	14
Pleurisy	12
Fatty liver	12
Apoplexy	8
Enteritis	6
Thromboembolic disease	5
Septicemia	6
Typhoid fever	3
Diphtheria	2
Malaria	1

Final Diagnosis (Neoplastic)	Frequency
Carcinoma	12
Stomach	4
Esophagus	2
Ovary	2
Colon and Rectum	1
Brain	2
Parotid	1
Sarcoma	1
Unknown primary	6
TOTAL	19

Final Diagnosis (Medicolegal)	Examples	Frequency
Poisoning	Carbolic acid, Paris Green (copper/ arsenic)	4
Malnutrition	Marasmus, rickets, pernicious anemia	10
Alcoholism	Cirrhosis or DTs attributed to alcoholism	10
Neuropsychiatric	Mania, psychosis	2
Asphyxiation	Suffocation, strangulation	4
Trauma	Fracture, lacerations	6
Therapeutic complication	Wound infection	3



Conclusions: The most frequent causes of death in this cohort match those reported by New York State in 1896-8. Average age at death, 42 years, was younger than U.S. life expectancy (46.3 years for men, 48.3 years for women). There was insufficient data to classify decedents' occupations and socioeconomic status. No major diagnostic errors were seen, accounting for changes in nomenclature over time.

27 ABO Blood Group and Pulmonary Thromboembolism: A Retrospective Review of 815 Medical Autopsies

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Background: The importance of the ABO blood group reaches far beyond routine therapeutic transfusion and organ transplantation. Previous studies have demonstrated an increased risk for thromboembolic events associated with non-O blood groups compared with individuals of type O blood. It has been hypothesized that the increased risk of thromboembolic events in non-O blood group individuals, is attributable to increased concentrations of von Willebrand factor and factor VIII. In one study, mean von Willebrand factor in each blood group were: O 75%, A, 105%, B, 117% and AB 123%.

Design: 815 medical autopsies were reviewed for anatomic diagnoses of pulmonary embolism (PE) between 2004 and 2017 to determine the incidence of non-O blood groups. Age, sex, race, blood type and past medical history diagnoses were documented. Regional 2010 US Census data was used as a control for racial distribution analysis. ABO blood group distributions were compared with ABO data from the Retrovirus Epidemiology Donor Study (REDS) database which consisted of 3.1 million allogeneic blood donors in the United States from 1991 to 2000. ABO and race distribution independence was analyzed with the Pearson's chi-squared test, with statistical significance set at P values ≤ 0.05.

Results: Of 815 autopsies, 85 (10.4%) had a final anatomic diagnosis of PE. Age ranged from 2 weeks to 96 years with a median of 48 years. 46 PE's were female and 39 were male **Table 1**. 62 PE's were African American and 22 were Caucasian (P<.001). When race was not controlled for, 21 O, 22 A, 8 B and 4 AB blood types were documented (n=55, P<.002). When controlled for race, African Americans had 15 O and 23 non-O blood types (n=38, P<.001) **Fig 1**. The top contributory causes were as follows: surgery (n=26), cardiovascular disease (n=16), infection (n=15), malignancy (n=5), hereditary thrombophilia (n=4) **Fig 2**.

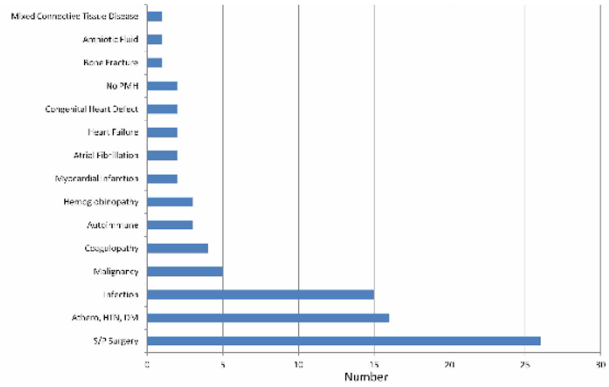
	Number
Autopsies	815
PE Anatomic Dx	85
Males	39
Females	46
African American	62
Caucasian	22
Latin/Hispanic	1
No Blood Type Recorded	30
Group O	21
Non-O	34

	African American and Caucasian Blood Group Distribution		
	PE Autopsies	United States	
Group O	21 34.14 (5.06)	2186433 2186419.86 (0.00)	2186454
Group A	22 14.79 (3.62)	946968 946975.21 (0.00)	946990
Group B	8 4.50 (2.73)	288005 288008.50 (0.00)	288013
Group AB	4 1.58 (3.72)	100991 100993.42 (0.00)	100995
	55	3522397	3522452

χ^2 = 15.028, df = 3, χ^2/df = 5.01, P(χ^2 > 15.028) = 0.0018

	African American Blood Group Distribution		
	PE Autopsies	United States	
Group O	15 34.46 (10.99)	1184971 1184951.54 (0.00)	1184986
Non-O	23 3.54 (106.87)	121802 121821.46 (0.00)	121825
	38	1306773	1306811

χ^2 = 117.864, df = 1, χ^2/df = 117.86, P(χ^2 > 117.864) = 0.0000



Conclusions: Non-O blood group incidence was statistically higher among autopsy PE's when compared to the US blood donor distribution. PE's among African Americans in our study was 2.8 times higher than that of Caucasians. In agreement with previous studies, we conclude the possibility that non-O blood types are at an increased risk for thromboembolic events. It is noteworthy that multiple contributory risk factors, were present in all but two PE's. A study with higher statistical power is worthy of investigational follow up for ABO blood group may have a potential role in the risk stratification of patients at risk for thromboembolic events.

28 Metastatic Breast Carcinoma to the Adrenal Gland: An Autopsy Review

Anam Naumaan[1], *Jayjay Z Blanco*, *Waqas Mahmud*[2], *Ritu Ghai*[3], *Pincas Bitterman*, *Vijaya Reddy*, *Paolo Gattuso*[4]. [1]Rush university medical center, Chicago, IL, [2]Rush university medical center, Chicago, Illinois, [3]Rush University Medical Center, Chicago, USA, [4]Burr Ridge, IL

Background: Invasive breast carcinoma usually spreads to bones, lungs and lymph nodes, while adrenal gland metastases are rarely seen in clinical practice. We present a retrospective autopsy study, which investigates the clinicopathologic findings and prognostic markers in patients with breast carcinoma showing adrenal gland metastasis at the time of autopsy.

Design: From 1993 to 2017 the pathology autopsy files at our institution were reviewed for a diagnosis of breast carcinoma. The clinical and pathologic data of all cases of breast carcinoma was revised in detail.

Results: A total of 228 cases of adrenal gland involvement by metastatic carcinoma were studied, of which 21 cases of metastatic breast carcinoma were found, with an age range of 34-78 years old (mean = 61.1 years). Of these, 8 (38.1%) had adrenal gland metastasis, along with metastasis to other common sites. 6 (75%) had bilateral adrenal gland metastasis, while 2 had unilateral metastasis to the left adrenal gland. Of the 8 cases with adrenal gland metastasis, 5 (62.5%) were negative for ER (estrogen receptor), PR (progesterone receptor) and Her2neu receptors, while 2 had weak ER positivity and were negative for PR and Her2neu. 1 case had both ER and PR positivity, and was negative for Her2neu. On follow-up, 6 (75%) patients with adrenal gland metastasis died within 5 years of initial diagnosis of breast cancer (range = 1-5 years), while 1 died 26 years later, and no data was available for one case regarding the time of initial diagnosis. Of the 6 patients which died within 5 years of initial diagnosis, 4 (66.7%) had bilateral metastasis and 5 (83.3%) were triple negative.

Conclusions: We conclude that 83% of metastatic breast carcinoma to the adrenal gland are triple negative, indicating an aggressive clinical course. 75% of the tumors involving the adrenal gland were bilateral metastasis; while no single isolated metastasis involving the adrenal gland was found, supporting its rarity. Adrenal gland metastasis is a rare clinical event and when present, may represent a systemic multiple organ spread of the tumor.

29 Pediatric Pulmonary Emboli at Autopsy: An Update and Case Series Review

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Background: Pulmonary embolus is a well-documented cause of death in adults, but less so in children. Blockage of the pulmonary vasculature by emboli disrupt the cardiopulmonary circuit and lead to cardiopulmonary arrest. The composition of pulmonary emboli vary, with the most common type in adults being the result of thromboemboli that form in the leg and travel to the lungs. However, the prevalence and types of fatal pulmonary emboli in the pediatric population are not well documented. A comprehensive retrospective database search of autopsy cases was performed to study the demographics, types, and circumstances surrounding fatal pediatric pulmonary emboli.

Design: A CoPath database search of autopsy reports performed at our institution from 1997-2017 was performed using the key words "embolus" or "emboli" and limited to patients from the age 0 to 18. Thirteen cases were identified. The histologic findings and histories were reviewed.

Results: Of the thirteen cases identified, eight (8/13, 62%) were male and five were female. The average age was 8.0 (range: 0-18). Approximately half of the emboli were thromboemboli (6/13, 46%), followed by septic emboli (3/13, 23%). There were three cases of fat/marrow emboli, and one case of foreign material emboli following spinal surgery consistent with Floseal hemostatic matrix. Six of thirteen cases (6/13, 46%) had a recent history of surgery (<2 weeks prior to expiration), while yet another three (3/13, 23%) were undergoing chemotherapy for a malignancy.

Conclusions: To our knowledge, this is the first case series to examine the demographics and types of pulmonary emboli in individuals 18 years old or less at autopsy. Like in adults, thromboembolization was a common type. However, unlike in adult pulmonary emboli, which are often associated with chronic disease processes, thromboembolization in children was frequently associated with acute disease processes (e.g. malignancy, sepsis, lung transplant, heart surgery). In addition, fatal pediatric pulmonary emboli were frequently preceded by surgical interventions. Informed awareness of the risks factors involved fatal pediatric pulmonary emboli may assist clinicians in the detection and treatment of pulmonary emboli.

30 Back to the Future: Network Analysis on Autopsy Generated Data Identifies Changes in Disease Patterns over 18 Years

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Background: Autopsies provide a unique opportunity to simultaneously assess coexisting diseases in a patient, including subclinical ones. Systems-level analysis of data produced at autopsy is underutilized by hospital administrations for quality improvement. We analyzed differences in autopsy-generated epidemiology between the years 1995 and 2012/2013. In addition, we used network analysis to identify changes in disease connectivity.

Design: Retrospective review of all adult autopsy reports at our institution from 1995, 2012 and 2013 was performed. The majority of autopsy pathologists (9/15) were consistent between years. Patient characteristics and each disease entity present in reports was recorded. 123 autopsies from 1995 and 261 from 2012-2013 were identified. Network analysis was performed on the two data sets. Spearman's coefficients were calculated for each pair of diseases. Those with significant correlation ($p < 0.01$) were used. Diseases with the highest connectivity (most disease associations) were identified.

Results: There were no differences in age or gender of patients between years. The mean number of diseases per autopsy, controlled for pathologist, was similar (5.6 and 5.8, p=0.61). A significant difference in disease prevalence was seen among few entities. In 1995, fungal pneumonia and HIV/AIDS were more common. In 2012/13, CNS neoplasms, diabetes, and decubitus ulcers were more common. No significant difference was seen among causes of death, although HIV/AIDS represented the second most prevalent cause of death in 1995 and the seventh in 2012-2013. In the 1995 network, diseases with highest connectivity were more likely to represent causes of death (e.g. intracranial hemorrhage, alcoholic liver disease) than 2012-2013, where the most connected diseases were infectious (e.g. UTI, sepsis).

Conclusions: We identify no significant difference in the number of diseases reported per autopsy over 18 years. Our data show differences which reflect known epidemiologic shifts (decreasing prevalence of HIV/AIDS) and less obvious ones such as an increasing rate of decubitus ulcers. The highly connected diseases have shifted from being major causes of death to infectious entities. This may represent an increased ability to treat the former, and an inability to control the latter. Network analysis as a tool to analyze autopsy-generated data may be useful to generate hypotheses about changes in hospital/treatment policies over time, and their effect on outcomes.

31 Death After Solid Organ Biopsy: An Autopsy Series.

David S Priemer[1], *Carrie Phillips*[2], *Oscar Cummings*[1], *Romil Saxena*[3]. [1]Indiana University School of Medicine, Indianapolis, IN, [2]Indiana University Health, Indianapolis, IN, [3]Indiana Univ/Medicine, Indianapolis, IN

Background: Biopsies of liver, lung, and kidney (LLK) are routinely performed for a variety of indications, including suspicion of organ dysfunction, mass lesions, and for monitoring of allograft function. In each case, biopsy diagnosis forms the basis of clinical management. However, the diagnosis depends on the area sampled, whether or not it is representative of the organ or lesion as a whole. When available, autopsies are an invaluable resource for assessing diagnoses issued from biopsies of solid organs. Also, although generally safe, LLK biopsies are associated with a number of possible complications, including death. Autopsies additionally represent an important tool for assessing the contribution of a biopsy procedure to patient mortality. This is particularly important in patients who die soon after a procedure.

Design: A search of our pathology database was performed from 1988 to 2016 to identify patients who were autopsied after dying within 30 days of either a needle or wedge biopsy of the liver, lung, or kidney. Concordance was determined by review of biopsy and autopsy reports. Finally, autopsy reports were reviewed to determine the extent to which biopsies contributed to patient deaths. Contribution of a biopsy to death was given a designation of 'unlikely' (biopsy did not appear to contribute to death), 'possible' (biopsy may have contributed to death), or 'probable' (death was influenced by or occurred as a result of biopsy).

Results: We identified 147 patients (87 male, 60 female). Average patient age was 50 years (range: 2 weeks-78 years). Time interval between biopsy and death averaged 10 days. Concordance between biopsy and autopsy findings, and contributions of biopsy procedures to patient mortality are shown in the **Table**.

	Liver (n=92)	Lung (n=45)	Kidney (n=10)	Overall (n=147)
Concordance (n)	95% (87)	71% (32)	90% (9)	87% (128)
Biopsy contribution to death				
Probable (n)	5% (5)	7% (3)	10% (1)	6% (9)
Possible (n)	11% (10)	7% (3)	10% (1)	10% (14)
Unlikely (n)	84% (77)	87% (39)	80% (8)	84% (124)

Autopsy can be used to validate findings of LLK biopsies and confirms that biopsies are accurate in most cases.

Autopsies performed soon after a patient receives an LLK biopsy reveal a considerable proportion of cases in which there is discordance with biopsy findings. This discordance is highest in the lung, followed by the kidney and liver.

LLK biopsies generally do not result in complications that contribute to patient mortality. In a minority of patients who die soon after the procedure, LLK biopsies may be responsible for complications that contribute to, and rarely precipitate, death. This study confirms a small but definite risk of death from a biopsy.

The autopsy is critical to determine the contribution of a biopsy procedure to death.

32 Mortality due to Cryptococcus neoformans and C. gattii in Mozambique: an Autopsy Study

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Background: Cryptococcosis is one of the main opportunistic infections and the leading cause of meningitis in HIV-infected adults in sub-Saharan Africa. Recent estimates indicate that cryptococcal meningitis account for up to 15% of AIDS-related deaths with more than 130,000 deaths occurring annually in this region. It has been suggested that many patients die without a correct diagnosis. Human cryptococcal infections were attributed to *Cryptococcus neoformans* until *C. gattii* was classified as a distinct species by molecular methods in 2002. The aim of this study was to characterize the clinical, pathological and microbiological features of a series of fatal cryptococcal infections from a large autopsy series of HIV-positive adults who died in Mozambique.

Design: Observational study in which a minimally invasive and a complete autopsy were performed to 109 HIV-1 positive patients who died at the Maputo Central Hospital in Mozambique. PAS and a specific real time PCR for *Cryptococcus spp.* were performed in all samples from the lungs, central nervous system (CNS), bone marrow, spleen, and liver. Plasma and cerebrospinal fluid (CSF) samples were tested by both real time PCR and cryptococcus antigen (CrAg) lateral flow test. Identification of cryptococcal species was carried out by amplification of the rRNA intergenic spacer (IGS) region, followed by forward and reverse sequencing of the amplicons.

Results: Fatal cryptococcal infection was confirmed in 11 (10%) of the patients. Six patients (55%) were women. Clinically, cryptococosis was diagnosed in only two patients (18%). 10/11 (91%) were disseminated infections and one (9%) was a localized meningoencephalitis. The percentage of involvement of the different organs was CNS 100%, lungs 91%, spleen 73%, bone marrow 64% and liver 55%. The microorganism was identified by PCR in the CSF in 82% and in the plasma 60% of the cases, but it was identified in all cases with CrAg lateral flow test. Eight (73%) of the fatal infections were caused *C. neoformans var grubii,* whereas three (27%) were caused by *C. C. gattii.* Minimally invasive autopsy identified all cases.

Conclusions: Cryptococcosis is a frequent clinically non-suspected cause of death in HIV-positive patients in sub-Saharan Africa. *C. gattii* might be responsible of about one third of all fatal cryptoccoccal infections in this setting.

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33 Neuropathological Findings on Autopsy: A Ten Year Retrospective Study From A Single Institution Experience

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Background: Over the past thirty to forty years there has been a drastic decline in the number of autopsies performed in the United States; one proposed reason being the ability to recognize and diagnose diseases with greater accuracy. Furthermore, a greater understanding of the pathology underlying these disorders play a key role in understanding the cause of death. Despite the decline in the number of autopsies, it continues to be a valuable tool for evaluating and understanding the pathogenesis of human disease; and to a greater extent, neuropathologic disorders. Although there have been many advances in diagnostic medicine, neuropathology continues to be a field not many are exposed to. Here we present a ten-year review of the neuropathological findings from 647 autopsies.

Design: This retrospective study was conducted by reviewing in-house autopsies performed at our institution during January 2008 - September 2017. Routine sections from the brain were preserved in 10% formalin fixation prior to being processed and examined microscopically. The findings for each case were sub-classified into no pathologic findings, hypoxic/anoxic changes, infarcts/hemorrhage, dementia, infectious, hydrocephalus, neoplasms, atherosclerosis/vascular disease, and others (Fig 1). SPSS v21.0 was used for data analysis.

Results: A total of 829 autopsies were performed (excluding outside

autopsies); 182 of which were omitted as these were non-neuro or autolyzed fetopsies. Of the 647 autopsies included in this study, 81 were Pediatric, 365 adults and 201 were geriatrics. The age rage included 1 day to 117 years with a male predominance (54%). In the majority of autopsies (34.6%) there were no pathologic findings, while the most common finding included infarcts/hemorrhage (17.8%). Age stratified analyisis; however, showed that hypoxic changes were the most common finding in the pediatric population and dementia in the geriatrics population (Fig 2). Vascular disease was a relatively common finding in the adult (6.3%) and geriatric populations (10.4%).

Fig. 1

Findings	Number (N=647)	Percentage
No pathological findings	224	34.6
Infarcts/Hemorrhage	115	17.8
Hypoxic/Anoxic changes	87	13.4
Dementia (Alzheimer's, Parkinson's, Lewy Body, etc.)	64	9.9
Atherosclerosis/Vasculitis	44	6.8
Neoplasms	30	4.6
Infectious (meningitis, encephalitis, ventriculitis, etc.)	20	3.1
Hydrocephalus (NPH, Aqueduct stenosis, etc.)	14	2.2
Others (ALS, MSA, OPCA, MS, hepatic encephalopathy, trauma, etc.)	49	7.6

IVH; Intraventricular Hemorrhage, CAA; Cerebral Amyloid Angiopathy, NPH; Normal Pressure Hydrocephalus, ALS; Amyotrophic Lateral Sclerosis, MSA; Multi-System Atrophy, OPCA; Olivo-pontocerebellar Atrophy, MS; Multiple Sclerosis.

Fig. 2

	Pediatric n=81	Adult n=365	Geriatrics n=201
No pathological findings	24 (29.6%)	154 (42.2%)	46 (22.9%)
Hypoxic/Anoxic changes	23 (28.4%)	51 (14%)	13 (6.5%)
Infarcts/Hemorrhage	18 (22.2%)	58 (15.9)	39 (19.4%)
Dementia	-	14 (3.8%)	48 (23.9%)
Infectious	3 (3.7%)	15 (4.1%)	2 (1%)
Hydrocephalus	2 (2.5%)	7 (1.9%)	5 (2.5%)
Neoplasms	3 (3.7%)	16 (4.4%)	11 (5.4%)
Atherosclerosis/Vasculitis	-	23 (6.3%)	21 (10.4%)
Others	8 (9.9%)	27 (7.4%)	16 (8%)

Conclusions: Autopsy continues to be a useful resource for the understanding of neurological disorders and various pathology of the central nervous system. This study highlights a variety of neuropathologic findings that may be found on autopsy, some of which were incidental and others which were a direct contributor to the cause of death. Neuropathology continues to be a complex field which can only be fully understood through post-mortem examination.

34 Autopsy findings in HIV/AIDS patients in Lago University Teaching Hospital: A one year prospective study

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Background: Nigeria has the second largest number of individuals living with HIV/AIDS in the world after South Africa and contributes about 9% of the global HIV burden. It has also been estimated that there are 336,379 annual new HIV infections and that about 192,000 of these individuals die of HIV/AIDS annually in Nigeria. Yet, there is a paucity of autopsy data among HIV/AIDS deaths in Nigeria. The objective of this study was to describe autopsy findings in HIV/AIDS cases in Lagos University Teaching Hospital, a tertiary health Centre in South-West Nigeria.

Design: This was a one year prospective descriptive study of all HIV1 and 2 positive cases referred for autopsy examination at the Morbid Anatomy department of Lagos University Teaching Hospital, Lagos, Nigeria.

Results: 754 autopsies were performed over the study period giving an autopsy rate of 33.1%. 44 patients (21 males and 23 females) were found to be HIV positive representing a prevalence of 5.8%. 23(53.3%) cases were diagnosed ante mortem while 21(47.7%) were diagnosed postmortem. The Patients age ranged from 6 hours to 69 years with a median age of 34 years.

Infections were seen in 27(61.4%) cases, out of which 13(48.1%) were AIDS defining infections. 8 (18.2%) of them had tuberculosis, 2 (4.5%) cases of non-tuberculous bacterial pneumonia, 1(2.3%) case each of cryptococcosis, Pneumocystis jiroveci pneumonia and progressive multifocal leukoencephalopathy (2.3%). Two (4.5%) patients had neoplasms (one case each of non-Hodgkin lymphoma and pleomorphic sarcoma, both with pulmonary and hepatic metastases at autopsy). Other causes of death included hypertensive heart disease, perforated strangulated right inguinal hernia, perforated ileo-ileal intussusceptions and penetrating perineal injury.

Conclusions: This study showed a demographic pattern of HIV infection comparable to previous national surveillance data but a higher HIV seroprevalence than the most recent national surveillance data.

Opportunistic infections were the most common cause of death in HIV infection and about half of HIV infected persons presented to the autopsy room undiagnosed.

35 Sudden Unexpected Infant death (SUID): Which is the Real Burden of SIDS?

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Background: Sudden unexpected infant death (SUID) is a major cause of death in infants <1 year of age. Sudden infant death syndrome (SIDS) is defined as a SUID that remains unexplained after complete post-mortem examination. An obligatory protocol of post-mortem examination has been introduced by law in Italy since 2014 to assess both the prevalence and etiopathogenesis of SIDS and implement research on the topic. Our aim was to compare SUID data before and after the application of a standard autopsy protocol of investigation.

Design: In the time interval 2004–2017, SUID cases occurring in the North-East of Italy, Veneto Region, excluding perinatal death, were referred to the Cardiovascular Pathology Unit. According to the national protocol, after 2014 death scene investigation, review of medical history, post mortem radiological examination and complete autopsy were performed, including gross and microscopic study with ultrastructural, toxicologic and molecular sampling. A neuropathological investigation of the brainstem was carried out in all cases. In presence of histological evidence of an infectious process, molecular tools (PCR and RT-PCR) were applied for detection of the following viruses (adenovirus-AV, parainfluenza, influenza A and B, respiratory syncytial virus-RSV, Epstein-Barr virus-EBV, cytomegalovirus-CMV, enterovirus-EV, human herpes virus 6-HHV6).

Results: A total of 37 SUID (27 M, mean age 3.44±3.60 months), 22 before and 15 after 2014, were collected. Of 22 autopsies performed during the period 2004-2013, 2 (10%) were SUID, both due to AV-related lymphocytic myocarditis, and 20 (90%) were SIDS. Among 15 SUID cases collected after 2014, SIDS accounted for 4 cases (27%), while a cause of death was found in 11 (73%) ($p< 0.0001$). In the 11 infants with a certain cause of death, the main findings were interstitial pneumonia and bronchiolitis with airway obstruction in 9 (82%) and lymphocytic myocarditis in 2 (18%). Molecular analysis was positive for viruses in 6/11 (54.5%) of cases.

Conclusions: Since the application of an obligatory protocol for SUID postmortem investigation, infective pulmonary or myocardial diseases have been the most common causes of 'explained' SUID, while SIDS accounts for about one fourth of cases. Efforts must be made to implement uniform autopsy protocols to provide reliable epidemiological data and to select real SIDS cases for genetic testing of cardiac-associated genes, with important implications for early diagnosis and prevention.

36 Post Mortem Assessment of Mortality and Liver Allograft after Orthotopic Liver Transplantation

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Background: Liver transplantation is the mainstay of treatment for numerous end stage liver diseases. Patient outcomes post transplant have steadily improved through refinement of the transplant procedure and antirejection regimens. The goal of this study was to evaluate factors still contributing to the mortality of liver transplant patients and assess the significance of allograft disease at death.

Design: The electronic database PowerPath was searched for autopsies of liver transplant patients from 2002-2017 at the University of Wisconsin-Madison. The report was reviewed for basic clinical information, gross findings and cause of death. Histologic sections of the allograft liver were assessed for acute and chronic rejection, other graft disease, and stage of fibrosis.

Results: Overall, 63 cases were included in the study. Males constituted 52% of the study population and ages ranged from 1 to 79 years (avg 50 yrs). The most frequent underlying liver pathologies were hepatitis B/C (27%) and alcohol (27%), followed by chronic cholestatic liver disease (11%), nonalcoholic fatty liver disease (10%), short gut syndrome (6%), autoimmune hepatitis (5%), and other (17%). Time of transplant to death ranged from 0 days to 22 years (avg 2.6 yrs) with 44% of deaths occurring more than 1 year from transplant. The most frequent causes of death included infection (46%), hypertensive and atherosclerotic cardiovascular disease (14%), hemorrhage due to coagulopathy (14%), and thrombosis (5%). Less common causes of death included stroke, post-transplant lymphoproliferative disorder (PTLD), and complications during liver transplantation. Acute and chronic rejection were each identified in one case. The remaining cases showed variable pathology, including steatosis (19%), parenchymal atrophy (8%), venous outflow obstruction (6%), and less frequently,

massive hepatic necrosis and PTLD. Advanced fibrosis (stage 3-4) was seen in 22% of cases of which the majority (57%) represented recurrent graft disease.

Conclusions: Complications of liver transplantation and immunosuppression remain major causes of mortality in liver allograft recipients both short and long term. Severe allograft disease is less common and typically related to recurrent underlying disease rather than allograft rejection. These results emphasize the infection risks in transplant recipients and the importance of recurrent graft disease. Autopsy remains an important tool to identify factors resulting in morbidity and mortality in transplant recipients.

37 Frequency and Classification of Death Certification Errors at an Academic Tertiary Care Facility: 2013-2016

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Background: Death certificates (DCs) are legal documents containing critical information. Despite the importance of accurate certification, errors remain common. Estimates of error prevalence vary between studies and error classification systems are often unclear. The objectives of the current study were to evaluate the frequency and type of DC errors arising at an academic medical center and identify potential systemic factors impeding certification accuracy.

Design: Autopsy reports and DCs for patients expiring under the care of our clinicians between 2013-2016 were retrospectively reviewed by 2 pathologists with forensic training. The cause/manner of death and other significant conditions reported on the DC were compared to those found at autopsy. Each pathologist independently classified DC errors via a 5 point scale of increasing error severity (FIgure 1). Cases with > 1 error were assigned multiple grades as needed. Discrepancies in error classification were tallied and final error grades assigned following case re-review. DC error frequency and type were analyzed. A systematic examination of the institutional death certification process was conducted.

Results: A total of 179 cases met inclusion criteria. All DCs were filled out by non-pathologist clinicians. In accordance with state statutes, certification occurred within 6 days of death pronouncement. No DC amendments were issued. Preliminary autopsy reports were finalized by forensic pathologists within 2 days of autopsy and final reports within an average of 30 days. The majority (85%) of DCs contained ≥ 1 error, with multiple errors (51%) being more common than single (33%). Of multi-error DCs, 78% had 2 errors, 21% had 3 errors, and 4% had 4 errors. In terms of error severity, the percentage of cases with both minor and major errors (35%) was almost the same as those with minor errors only (34%). Major error-only cases comprised a minority (17%). The most frequent error type was Grade 1 (53%), followed by Grade III (30%) and Grade IIb (18%). The more severe Grade IV errors were seen in 23% of cases; no Grade V errors were found.

Figure 1: Grading of Clinician Death Certificate Errors

	Error Grade	Error Description
Minor Errors	0	No Errors
	I	Other significant conditions (OSC) omitted or inappropriately attributed
	IIa	Part 1 diagnoses in illogical order or inclusion of diagnosis as a comorbidity but better classified as an OSC
	IIb	Nonspecific diagnosis listed as COD or as a factor contributing to death
	IIc	Minor missed comorbidities contributing to death or major comorbidity included as OSC
Major Errors	III	Major missed comorbidities contributing to death
	IVa	No acceptable underlying cause of death in Part I (ie. Mechanism only)
	IVb	Wrong cause of death (COD)
	V	Wrong manner of death (MOD)

Conclusions: These results suggest that DC errors may be more frequent then previously reported. By understanding the types of errors occurring on DCs, academic institutions can work to improve certification accuracy. Better clinician education, coordination with hospital risk management, and implementation of a systematic approach to ensuring concordance of DCs with autopsy results is recommended.

38 Snyder-Robinson Syndrome: An Autopsy Case Report

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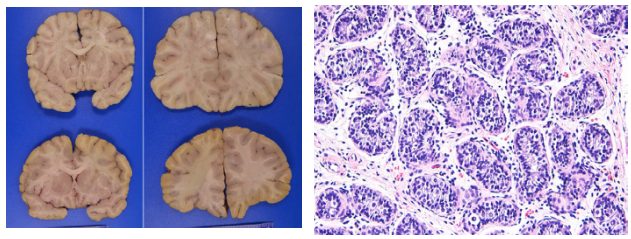
Background: Snyder-Robinson syndrome (SRS), also known as spermine synthase deficiency, is an X-linked recessive disorder which disrupts normal cell growth and development in a wide range of tissues. First described by Drs. Snyder and Robinson in 1969, SRS is characterized by intellectual disability, asthenic body habitus, facial dysmorphism, broad-based gate, and osteoporosis with frequent fractures. Approximately 67% of patients develop seizures; an imaging study showed increased total brain volumes, although some patients have normal imaging and electroencephalogram studies. No autopsy reports of this syndrome have been published to date.

Design: We report a pediatric autopsy of a 4-year-old male diagnosed with SRS due to a novel SMS gene mutation (p.L277F). Clinical symptoms included a history of intellectual disability, gait abnormalities, multiple fractures, and pharmacoresistant myoclonic epilepsy. Autopsy examination included complete external, internal, and neuropathologic examinations. Internal examination was somewhat limited due to organ donation.

Results: Autopsy examination showed a tall male child (>95 percentile height) with dysmorphic features including prominent cupped ears, protruding lower lip, and high-arched palate. Musculoskeletal abnormalities including an asthenic build and kyphosis were seen. Striking macrocephaly and megalencephaly were present (2840 gram brain). Microscopic examination of the brain revealed diffuse, predominantly acute, hypoxic/ischemic changes and hippocampal pathology consistent with the patient's history of epilepsy. There was microrchidia (1.3 cm average length; 2 cm expected length) with Leydig cell deficiency.

Figure 1. Coronal sections of SRS patient (top) compared with aged-match control (bottom).

Figure 2. H&E stained section of testes with tubules consisting of Sertoli cells and spermatogonium.



Conclusions: SRS is a rare disorder, but it is important to recognize. The reliance on recognition of clinical findings and genomic sequencing in order to make the diagnosis has likely resulted in under-diagnosis. The syndromic facies, musculoskeletal abnormalities, and multiple fractures are likely to prompt forensic pathologists to search for a unifying diagnosis at the time of autopsy. Therefore, clinicians and pathologists should be aware of SRS in order to properly identify, manage, and counsel patients and families.

39 Proteus-Like Syndrome with Unusual Hamartomatous Manifestations: An Autopsy Case of an 11-Year-Old Female

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Background: Proteus syndrome is an exceedingly rare condition characterized by asymmetrical overgrowth, hamartomas, and certain musculocutaneous abnormalities, often presenting between ages 6-18 months, and progressing to premature death. Previously defined by a constellation of these clinical findings, recent investigation identified a somatic mosaic mutation in AKT1 as the cause of Proteus syndrome, with clinical mimickers caused by mutations in PTEN and other genes. An 11-year-old female with clinically-diagnosed Proteus syndrome, worsening cardiopulmonary functional status with unusual lipomatous myocardial infiltration on echocardiogram, and an enlarging adnexal mass presented for oophorectomy, complicated by post-operative respiratory distress, cardiac arrest, and death on post-operative day one.

Design: The decedent underwent a complete unrestricted autopsy including external and internal gross examination, as well as histologic evaluation including special stains and immunohistochemical studies.

Results: Autopsy findings included features consistent with Proteus syndrome including stereotypical facies, asymmetric overgrowth with right-side predominance including leg length discrepancy

(10 cm) and overgrown digits, cerebriform connective tissue nevi, and epidermal nevi, and cerebral capillary telangiectasias. Additional findings included global severe lipomatous infiltration of myocardium, markedly asymmetric lungs (right 1040 gm, left 467 gm) with extensive hamartomatous fibrotic overgrowth and a right-sided alveolar adenoma (4 cm); and lipomatous infiltration of right-sided skeletal muscles. The adnexal mass removed ante-mortem demonstrated serous borderline tumor.

Conclusions: The most striking findings in this autopsy case of Proteus-like syndrome were global myocardial lipomatous infiltration, extensive hamartomatous fibrotic overgrowth of the lungs, and a 4 cm alveolar adenoma, in addition to the more usual musculocutaneous and vascular findings exhibited. While generalized lipomatous dysregulation and lung bullae are well-described in Proteus syndrome, this patient's overwhelming cardiopulmonary involvement by the disorder is unlike usual cases, and significantly contributed to her poor functional status and demise. Of note, genetic testing for AKT1 mutation was initiated ante-mortem and remains pending. In summary, this case demonstrates an unusual and devastating manifestation of Proteus-like syndrome, which may prove to be true Proteus syndrome, pending AKT1 status.

40 Fatal Varicella-Zoster Viral Hepatitis in a Patient with Hypothyroidism and without Immunodeficiency: An Autopsy Case

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Background: Severe hepatitis caused by a primary or recurrent varicella-zoster virus (VZV) infection is extremely rare, often fatal and occurs almost exclusively in immunocompromised individuals.

Design: A 44-year-old woman presented with altered mental status shortly after developing a skin rash. She had no prior history of VZV infection and had recent contact with a family member with shingles. Her encephalopathy and blood chemistry (AST 3,390, ALT 1,512, total bilirubin 3.0) indicated acute liver failure. Skin biopsy with immunohistochemistry and blood PCR established VZV infection. Hypoxemia and procalcitonin level (13.4 ng/ml) suggested septic shock. Of note, her free T4 was undetectable, and TSH was 20.23 mIU/L. She died on the second hospital day.

Results: Gross autopsy findings included: a widely distributed papulovesicular skin eruption; a 3,260 g liver with red macules on the surface and red-yellow mottling on section; 2,020g (combined) lungs with scattered red surface macules; linear, shallow esophageal ulcers; a 20 g symmetric, homogeneous thyroid. By microscopy, the liver contained areas of necrosis that appeared to extend from portal tracts with only rare classic inclusions, no inflammatory cell infiltrate, and abundant karyorrhectic debris. Similar small necrotic lesions were present in lymph nodes and the thyroid that also showed the changes of Hashimoto thyroiditis. The lungs contained small areas of necrosis without inflammatory cells or conspicuous cellular inclusions. The necrotic areas in all organs stained with antibodies to VZV. The lesions in the skin and the esophagus showed typical cytopathic changes without inflammatory cells.

Conclusions: This nearly unique report of a case of fatal VZV hepatitis with only hypothyroidism as possible predisposing factor follows epidemiologic studies (Int J Infect Dis. 2017;59:90 and Epidemiol Infect.2015;143:3557) that suggested thyroid hormones confer resistance to VZV infection.

41 Utility of Pre-Treatment with Osmium Tetraoxide for Histologic Identification of Fat Emboli: An Autopsy Case Series in Sickle Cell Disease

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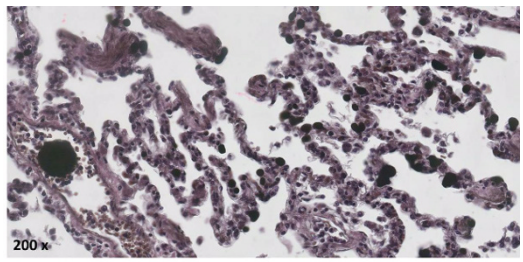
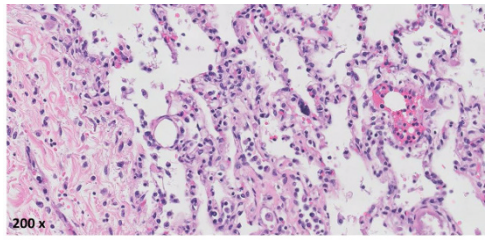
Background: Sickle cell disease (SCD) is associated with many complications including vaso-occlusive pain crises and acute chest syndrome. The fat emboli syndrome (FES) represents a rare but potentially fatal sequela of bone marrow necrosis in SCD. Failure of bone marrow microcirculation in SCD and possibly even sickle cell trait can lead to marrow infarction and subsequent release of fat emboli. Identification of fat emboli in pulmonary and cerebral microvasculature can be challenging and easily missed on routine hematoxylin and eosin (H&E) stain. Osmium tetroxide pre-treatment of formalin-fixed sections, known as osmication, may improve identification of fat emboli in SCD.

Design: Complete autopsies were performed on two adults with reported Hemoglobin (Hb) SS SCD and one adult with suspected sickle cell trait. Each decedent exhibited acute respiratory distress with negative cardiac workup. Formalin-fixed lung and brain sections underwent osmication for preservation of lipid during processing. Additional lung sections from two non-SCD autopsy cases were obtained as negative controls for osmication, one case without history of cardiopulmonary resuscitation (CPR) and one case after CPR.

Results: Osmicated histologic sections from all three autopsies demonstrated diffuse, black-stained fat emboli in the pulmonary microvasculature (Figure 1) and in the cerebral cortex in two cases. As compared to H&E stained sections (Figure 2), fat emboli were significantly easier to identify, and their burden was better appreciated. Both controls did not reveal fat emboli. Clinical characteristics and summary of autopsy findings are reported (Table).

	Case #1	Case #2	Case #3
Age (years)	22	34	78
Sex	Female	Female	Male
Reported/Suspected SCD	HbSS	HbSS	Possible HbS trait
High-Performance Liquid Chromatography (HPLC) showing approximate baseline Hb profile without transfusion (%HbA/ HbA2/HbF/HbS)	2.0 / 5.4 / 2.7 / 89.7 (one month before death)	3.9 / 4.5 / 3.5 / 86.8 (two months before death)	N/A
Hb (g/dL) and MCV (fL) on day of HPLC	7.5 g/dL 68 fL	6.9 g/dL 83 fL	9.3 g/dL 76 fL (day of death)
CPR	Yes, rib fractures absent	Yes, rib fractures absent	No
Lungs	Diffuse fat emboli with alveolar inflammation and necrotic marrow elements	Organizing microscopic thromboemboli, diffuse fat emboli and necrotic marrow elements	Diffuse fat emboli, prominent sickled erythrocytes in microvasculature
Bone marrow	Left-shifted myeloid maturation, diffuse hemophagocytosis	Extensive sickled erythrocytes	Erythroid and myeloid hyperplasia with left shift
Spleen	Enlarged (493 g) with Gamna-Gandy bodies, hemophagocytosis	Absent, likely autoinfarcted	Shrunken (44 g) with fat emboli
Brain	Cortical fat emboli	No cortical fat emboli	Cortical fat emboli





Conclusions: Histologic identification of fat emboli is substantially aided by osmication of formalin-fixed tissue in autopsies performed on patients with SCD or sickle cell trait. Given the relative underdiagnosis of FES, osmication may assist in more accurate autopsy diagnoses. Of note, retrospective review of Hb evaluations from the two younger decedents revealed elevated levels of HbA_2 and very low

HbA suspicious for the S/^{0} compound heterozygote state, which has been reported to confer an increased risk of fat embolism related to bone marrow necrosis. Persistent splenomegaly in the youngest decedent may further support this possibility. Identification of fat emboli interspersed with larger marrow elements, cerebrovascular involvement, and an absence of rib fractures are more characteristic of an etiology related to hemoglobinopathy rather than CPR.

42 Clinicopathologic Findings and Outcomes in Shone Complex

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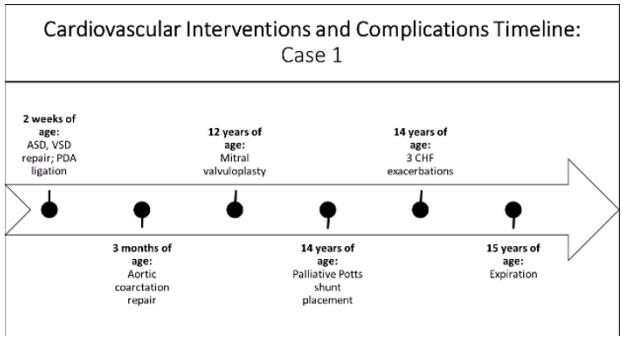
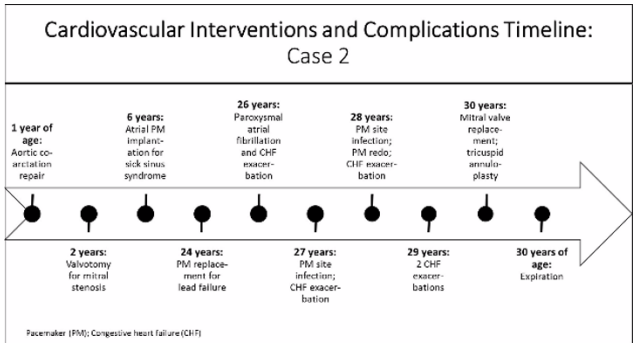
Background: Shone complex (SC) is an exceptionally rare congenital heart disease (CHD), with an incidence of 0.6% of all CHDs. Described in 1963, it classically consists of 4 left heart anomalies: supravalvar mitral ring, parachute mitral valve, subaortic stenosis, and aortic coarctation. Incomplete forms of SC are more often seen and consist of at least 1 form of left ventricular (LV) inflow tract defect and at least 1 LV outflow tract defect. Due to its rarity, only limited data regarding long term outcomes and causes of death (COD) are available. Our objective is to further characterize this disease and provide additional data on these metrics.

Design: A 10-year search of our autopsy database for "Shone" was performed. All hospital records were reviewed, including final autopsy reports and histologic sections. We identified cause of death, cardiovascular (CV) interventions and complications, initial cardiac defects, and comorbidities.

Results: Two cases of incomplete SC were identified, Case 1 with a 15-year duration follow-up and Case 2 with 30 years of follow-up. Timelines of lifelong CV interventions and complications are shown in Figures 1 & 2. Initial cardiac defects and comorbidities are described in Table 1. The immediate COD in Case 1 was acute right ventricular heart failure complicated by respiratory failure secondary to diffuse alveolar damage, pulmonary vascular hypertension, and focal bronchopneumonia. The immediate COD in Case 2 was acute biventricular heart failure complicated by post-surgical cardiac tamponade and respiratory failure secondary to pulmonary vascular hypertension and pulmonary edema

Case Characteristics	Case 1	Case 2
Male sex	✓	
Initial Shone complex lesions		
Supravalvular mitral ring		
Parachute mitral valve with stenosis	✓	✓
Subaortic stenosis		✓
Aortic coarctation	✓	✓
Other initial cardiac lesions		
Hypoplastic ascending aorta and aortic arch	✓	
Hypoplastic aortic valve with aortic stenosis	✓	
Bicuspid aortic valve		✓
Small aortic valve	✓	
Atrial septal defect	✓	
Ventricular septal defect	✓	
Patent ductus arteriosus	✓	
Hypoplastic left ventricle and left ventricular outflow tract	✓	
Initial cormorbidites		
Pulmonary hypertension	✓	✓
Hirschsprung's disease	✓	
Acquired comorbidities		
Recurrent respiratory infections	✓	✓
Massive mediastinal and retroperitoneal lymphadenopathy	✓	✓
Sarcoidosis		✓
Cor pulmonale	✓	✓
Immune thrombocytopenic purpura		✓
Cardiac cirrhosis	✓	✓
Sick sinus syndrome		✓
Paroxysmal atrial fibrillation		✓
Chronic kidney disease		✓





Conclusions: We identified 2 autopsy cases of incomplete SC in a tertiary medical center over a 10-year timeframe. The patients from our series presented shortly following birth and required multiple surgeries throughout their lives. There was substantial morbidity and mortality secondary to arrhythmias, cor pulmonale, pulmonary infection, and late-course interventions. Increased recognition of SC and its long-term complications will hopefully allow for finer adjustment of clinical care and prognostication.

43 Autopsy and Immunohistochemical Findings in Intravascular Synovial Sarcoma

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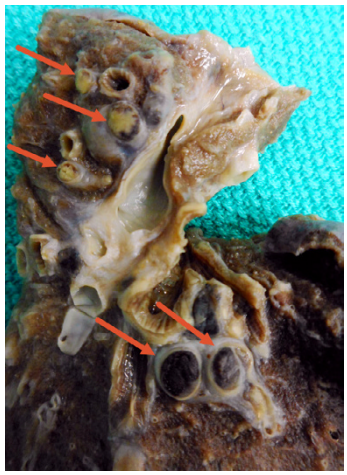
Background: Intravascular synovial sarcoma (IVSS) is an exceedingly rare mesenchymal neoplasm with only 12 cases documented in the literature. It tends to affect young adults and the femoral vein is the most common primary site. Clinical symptoms include pain and swelling of the affected extremity, sometimes with sudden or progressive dyspnea from pulmonary emboli.

Design: We report an autopsy of a 60-year-old female who presented to the Emergency Room following a syncopal episode. Work up showed a saddle pulmonary embolus. Lower extremity sonography revealed lack of normal venous blood flow and compressibility in left common femoral, deep femoral, and superficial femoral veins with nonocclusive thrombus in left external iliac and popliteal veins. She underwent salvage embolectomy and veno-arterial extracorporeal membrane oxygenation (ECMO). Pathologic examination of the pulmonary embolus revealed a malignant neoplasm. Computerized tomography revealed a 5.9 x 4.5 cm soft tissue mass in the left groin but no other possible primary tumor sites. She had persistent pulmonary hypertension and was unable to be weaned from ECMO.

Results: Autopsy findings included pulmonary tumor emboli, hemorrhage and infarct (Figure 1). Left inguinal tissue revealed hemorrhage and reactive lymphadenopathy. No mass lesions were identified in organs or body cavities. Microscopy of tumor emboli showed monophasic, round to elongated malignant cells with scant to moderate eosinophilic cytoplasm arranged in sheets, vague fascicles, and hemangiopericytomatous patterns. No glandular structures were

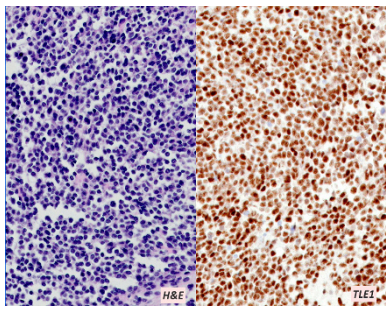
seen. By immunohistochemistry, malignant cells were positive for CD99, EMA, and transducin-like enhancer of split 1 expression (TLE1) (Figure 2). Cytokeratin and endothelial markers were negative. The cause of death was IVSS with extensive pulmonary tumor emboli.



Conclusions: The diagnosis of IVSS is established by morphologic and immunohistochemical features. While TLE1 is used as a marker for synovial sarcoma, TLE1 positivity is also seen in other mesenchymal tumors and tissues, and whether IVSS truly represents a tumor of synovial origin is debatable. Our autopsy demonstrates the diagnostic and therapeutic difficulties associated with IVSS.

44 Fatal Spontaneous Tumor Lysis Syndrome from Untreated Metastatic Colorectal Adenocarcinoma: An Autopsy Case

Mark Zivney[1], *Lindsay Taute*[2], *Emerson Y Chen*[2], *Peter Stenzel*[2].



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Background: Tumor lysis syndrome (TLS) is caused by massive death of tumor cells with the release of intracellular contents into the bloodstream. The resulting hyperkalemia, hyperuricemia, hyperphosphatemia and lactic acidosis precipitate a life-threatening emergency. TLS most often occurs following chemotherapy of hematologic malignancies. Less commonly TLS occurs spontaneously, in the absence of tumoricidal therapy. TLS in cases of solid tumors is very rare; spontaneous TLS in solid tumors is exceedingly rare.

In a previously described case report of spontaneous TLS in metastatic colorectal carcinoma, the patient survived the acute episode (Am J Med Sci 2003;325:38-40).

Design: We report an autopsy case of a 47-year-old woman with recently diagnosed colorectal adenocarcinoma metastatic to the liver. The patient presented with abdominal pain. Imaging revealed innumerable liver lesions and a lesion in the sigmoid colon. Liver biopsy showed an adenocarcinoma that expressed CDX-2 and cytokeratin 20, consistent with a colonic origin. Following admission, she developed hyperuricemia (23.1 mg/dL), hyperkalemia (5.9 mmol/L), hyperphosphatemia (8.1 mg/dL), and lactic acidosis (6.4 mmol/L). Subsequently, she developed acute renal failure, shock, and arrhythmia. Despite dialysis and bicarbonate infusions, her metabolic acidosis worsened and she died.

Results: A 7 cm exophytic ulcerated transmural mass in the sigmoid colon extended to the serosa; histology revealed a poorly differentiated carcinoma with extensive necrosis. The 5860 g liver appeared variegated red and yellow on the surface and on section. Microscopic examination showed a mixture of hepatic parenchyma (necrotic in areas) and abnormal areas similar to the colon tumor. The tumor expressed CDX-2 and cytokeratin 20. Tumor and thrombi were frequent in portal vein radicals. Microscopic metastases were present in the lungs.

Conclusions: The pathologic features that possibly contributed to the development of fatal tumor lysis syndrome in this case include a large tumor burden in primary and metastatic sites, high grade malignancy, and perhaps most importantly, extensive invasion and thromboses of intrahepatic portal vein branches.