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PLATFORM and POSTER PRESENTATIONS

Autopsy

1 To Assess the Use of Ancillary Studies in the Determination of Cause of Death

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Background: Our institution has a busy adult autopsy practice, situated in West Dublin, with a catchment area of almost one quarter of a million people. Approximately 270 autopsies are performed annually. Histology is taken routinely in all autopsies, with additional studies (toxicology, neuropathology, microbiology) being undertaken in specific cases, as per the guidelines of the Royal College of Pathologists. Due to the paucity of literature regarding the use of microbiology sampling in adult autopsy practice, a particular emphasis was placed on investigating the contribution of microbiology in the determination of cause of death.

Design: This case series includes all adult autopsies performed in our institution over a 2-year period. Basic demographics and clinical details including location of death (in-hospital, out of hospital) were recorded. The use of additional studies was recorded. Final reports were then compared with provisional and interim reports to evaluate the contribution of each additional study.

Results: 500 autopsies were carried out (35% female; 65% male). 21% of deaths occurred in the emergency department, 45% in hospital and 34% out of hospital. Microbiology testing, including blood cultures and tissue swabs, was carried out in 15% and toxicology was carried out in in 52% of cases.

Provisional reports were issued in 73% of cases, with determination of cause of death deferred pending additional studies in 27%.

Cause of death was changed in 13% of cases based on histology, toxicology or combined histology/toxicology results.

In cases in which determination of cause of death was deferred, histology established cause of death in 76%, toxicology in 16%. The remaining 8% consisted of cases in which cause of death was established by neuropathology or those in which no anatomic cause of death was established.

While microbiology did not alter cause of death, it was contributory in 5.5% of cases but was, however, under-utilised in cases of presumed sepsis.

Conclusions: Histology was the most common reason for change of cause of death, justifying its routine use. Microbiology was under-utilised, especially in deaths presumed to be due to both hospital-acquired and community-acquired sepsis, in the appropriate clinical setting. Further prospective analysis is required to fully assess its role as an adjunct in the evaluation of cause of death. Toxicology was useful in determination of cause of death in out-of-hospital deaths and neuropathology was useful in confirming cause of death, but rarely contributed if no other anatomical cause was found.

2 1971 Non-Atherosclerotic Sudden Cardiac Deaths Referred for Specialist Opinion to a Tertiary Centre in the UK during 1994-2010

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Background: Sudden cardiac death (SCD) from non-atherosclerotic causes is rare but is becoming increasingly recognised when it prematurely takes the life of an individual who is otherwise healthy and is of major importance because it often includes genetic diseases. There have been recent reports on sudden death based on extrapolations from death certificates and public media reports, the accuracy of which have been questioned due to a lack of an autopsy review. We report the results of the largest series to date of SCD with examination of cardiac tissue following a systematic protocol in a tertiary referral centre.

Design: Sudden cardiac death was defined as an unexpected sudden death within 1-24h of symptom onset. Case selection was performed to exclude cases of significant atherosclerotic disease, congestive heart failure, infant (≤1 year) and postoperative death or when toxicology was considered to have contributed to the death. Cases were retrieved in the period 1994-2010 and organised into 2 age groups: 1-35 years and ≥36 years.

Results: 1971 cases were retrieved with a male predominance (n=1263, 64%), median age 33 (range 1-98) years and predominately young (1-35 years); n=1107, 56%. A morphologically normal heart indicating Sudden Arrhythmic Death Syndrome (SADS) and channelopathy was the single leading cause of death (n=998, 51%). Cardiomyopathy accounted for almost a third of the deaths (n=578, 29%), with LVH (n=210, 11%), HCM (n=132, 7%) and ARVC (n=84, 4%) as the most significant contributors.

Conclusions: This large case series highlights the importance of SADS as the major cause of SCD particularly in the young, followed by cardiomyopathy. SCD organ retention and referral to specialist cardiac pathologists must be regarded as the 'gold standard'. When the autopsy identifies SADS or cardiomyopathy, the families of victims should be referred for cardiological screening since a significant proportion of these conditions are inherited.

3 Well's Scores Accurately Predict Presence of Massive Pulmonary Thromboembolism at Autopsy

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Background: Well's scores are utilized clinically to predict risk for pulmonary thromboembolism (PTE). Radiographic correlative studies have confirmed a high negative predictive value (NPV). This is the first autopsy study correlating Well's scores with PTE.

Design: A retrospective analysis of 85 adult autopsies from 2009 to 2011 was performed. Three cases were excluded due to inability to calculate Well's score due to death on arrival to hospital. Well's criteria were derived from chart review [clinical signs and symptoms of deep vein thrombosis (DVT), PTE first on differential diagnosis, heart rate > 100 bpm, immobilization ≥ 3 days or surgery in the previous four weeks, previous DVT or PTE, hemoptysis, and malignancy within 6 months]. Final autopsy reports were evaluated for presence or absence of PTE. Cases were classified by Well's score using the Clinical Decision Rule (CDR) [≤ 4, PTE unlikely; > 4, PTE likely]. Final autopsy reports were reviewed to classify cases as massive PTE (mPTE) with large saddle thromboemboli as cause of death, other PTE (oPTE) with small acute or chronic PTE that played a contributory role but were not sole cause of death, and negative PTE (nPTE) with no autopsy evidence of massive or other PTE.

Results: 85 autopsies with 11 PTE were studied, 3 were mPTE and 8 were oPTE. CDR accurately identified mPTE cases as likely for PTE. The oPTE all were classified as unlikely for PTE (false negative). For mPTE the CDR has a high NPV (100%) and a positive predictive value (PPV) of 23%. Detailed analysis of the ten falsely positive CDR revealed underlying malignancy (4), clinical signs of DVT (5), and positive DVT in the past (6) as the most prevalent criteria for the elevated score. The oPTE group (false negatives) contained 8 patients with CDR 1.5-4. Applying CDR to all PTE (oPTE plus mPTE) yielded a NPV of 89% and PPV of 23%.

Conclusions: Well's CDR is an effective tool used clinically for excluding acute PTE. This study confirms a high NPV for mPTE (100%) that decreases to 89% when including all PTE. Common causes for falsely elevated CDR include underlying malignancy, prior DVT, and clinical suspicion for DVT. This first autopsy study confirms the utility of Well's CDR to assess PTE risk. It is particularly useful for screening for massive PTE and less useful for smaller/chronic PTE. This study also shows that new clinical tools may help guide post-mortem investigations, potentially facilitating less invasive exams (virtopsy). This is a first post-mortem analysis of such a clinical tool, the Well's Criteria for pulmonary thromboembolism.

4 Does Genotyping for Warfarin Sensitivity Save Lives? A Study of Individuals on Warfarin Who Died of Bleeding

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Background: Warfarin is an anticoagulant with a narrow therapeutic window and potentially catastrophic consequences outside of that window, such as stroke, myocardial infarction, or intracerebral hemorrhage. Establishing an appropriate dose is challenging due to interindividual variability according to genetics, body size, age, and sex.

Two genes predict optimal warfarin dose. First, cytochrome P450 enzyme 2C9 (CYP2C9) metabolizes warfarin. Variants of CYP2C9, CYP2C9 *2 and CYP2C9 *3, reduce warfarin clearance. Second, vitamin K epoxide reductase complex (VKORC1) recycles vitamin K needed for clotting factors, and is the pharmacologic target of warfarin. Although it is well established that CYP2C9 and VKORC1 alleles account for about one third of interindividual dose variability, data comparing clinical outcomes using genotype guided dosing versus standard dosing is scant. Most studies report a primary endpoint of percent INR values outside the target range because serious bleeding events are rare, thus difficult to measure.

Design: Our aim was to determine the frequency of CYP2C9 and VKORC1 variant alleles in people who died of bleeding or related complications while taking warfarin. Autopsy files at the medical investigator's office were searched and 82 subjects were

identified. DNA was extracted from available specimens. Portions of CYP2C9 and VKORC1 genes containing relevant polymorphisms were amplified by PCR. Amplicons were analyzed by high resolution melting, and genotypes were determined by comparing subject melting curves to known controls. Frequencies of alleles were compared to those in the general population, matched for race, as published in medical literature.

Results: 82 subjects were genotyped, including 59 non-Hispanic white and 19 Hispanic white decedents. The frequency of CYP2C9 *2 was significantly higher in both groups than in the general population (non-Hispanic, 0.45 versus 0.16, $p = 3.3 \times 10^{-14}$; Hispanic, 0.28 versus 0.08, $p = 0.0021$). The frequency of CYP2C9 *3 was not different. The frequency of the VKORC1 warfarin sensitive haplotype trended higher in non-Hispanic whites (0.45 versus 0.38, $p = 0.17$) and achieved significance in Hispanic whites (0.72 versus 0.45, $p = 0.001$).

Conclusions: Variant alleles conferring enhanced sensitivity to warfarin are overrepresented in the sample population compared to the general population. Therefore, warfarin sensitive genotypes are associated with increased risk of death in people taking warfarin. Whether genotyping would have prevented deaths cannot be determined by the present study, and warrants further investigation.

5 Histopathologic Evaluation of In-Stent Restenosis at Autopsy in Patients with Coronary Stents

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Background: Pathologic evaluation of stented coronary arteries at autopsy is labor-intensive. There is no standardized technique for evaluation of stented coronary arteries, and plastic processing requires specialized techniqes. The objectives of this study were to assess the impact of in-stent findings on the final cause of death using paraffin based histologic methods.

Design: We retrospectively studied histologic findings of 87 intracoronary stents from 45 autopsy hearts (35 medical examiner and 10 hospital cases). There were 37 men (59 ± 13 years) and 8 women (64 ± 13 years). Stented arteries were radiographed and decalcified. Stents were removed using microdissection with tungsten carbide scissors or electrolysis. Sections were embedded and processed in paraffin. Restenosis was defined as >75% vessel narrowing as determined morphometrically. Thrombosis and fibrin deposition were documented in each case.

Results: There were 23 Taxus, 21 Endeavor, 10 Cypher, 9 RX Achieve, 6 Xience, 5 MultiLink Vision, 4 MuitiLink Rx, 3 NIR, 3 Palmaz Schatz, 2 AVE GFX, and 1 undetermined stent type. 85 were in native arteries, and 2 in vein grafts. 54 stents were successfully dissolved, 2 were microdissected after unsuccessful electrolysis, and 31 were microdissected. Of 5 patients with recent stent placement, causes of death were acute thrombosis of non-stented artery (2), in-stent thrombosis (1), complications of myocardial infarction (MI, 1) and iatrogenic right ventricular puncture (1). Of the 40 patients with only chronic stents, causes of death were noncoronary (24; 16 unnatural), and coronary (21; 13 sudden cardiac death). Of 32 stents in the coronary death group (CDG) after chronic stent placent, 8 had in-stent restenosis (25%) vs. 5 of 45 in the non-coronary death group (NCDG) (11%, p=0.1); mean percent stenosis was 45% vs. 35%, respectively (p=0.1). Two thrombi were found, one organizing in a vein graft in the NCDG, and one organized occlusive thrombus in the CDG. There were 2 fibrous total occlusions in the CDG and 1 in the NCDG. The rate of arrhythmogenic substrates (healed MI, cardiomegaly) was similar in the CDG and NCDG.

Conclusions: In this study, 1 of 5 deaths in the acute group was related to the stent, and no acute late-stent thromboses were found. There is a mild non-significant increase in restenosis and neointima in coronary deaths vs. non-coronary deaths. The cause of death is rarely impacted by in-stent findings at autopsy.

6 Rapid Autopsy Program for Pancreatic Carcinoma: Correlation of Histologic Subtypes and Pattern of Spread with Mucin Phenotype and Molecular Markers

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Background: Pancreatic ductal adenocarcinoma (PDA) is the 4th leading cause of cancer-related death with 1 and 5 year survival rates of 20-40% and 5%, respectively. Only 20% of patients are surgical candidates and 70% have metastatic disease at resection. Histology alone does not adequately predict biologic behavior or response to therapy. Novel molecular markers may aid in early diagnostic and therapeutic options. This study reports the morphologic variation and metastatic pattern of PDA in decedents enrolled in our rapid autopsy program (RAP) with correlation to mucin phenotype and other molecular markers associated with tumor progression.

Design: A trunk-only autopsy was performed via a modified Virchow method within 3 hours of death. Tissue was submitted for histopathology and snap frozen for the tissue bank. Photographs were taken to document extent of spread. All autopsy slides and reports were reviewed for histologic features and metastatic patterns. Tissues were analyzed by immunohistochemistry (IHC) for the expression of 18 different mucins and associated glycans previously linked with PDA. IHC staining intensity and percentage of positive cells was scored, converted to a heat map, and compared to histology and pattern of metastatic spread.

Results: Forty-eight patients with PDA were autopsied (2002-2011, mean postmortem interval 2.1 hrs). Degree of differentiation was well (5), moderately (18), and poorly (13) differentiated, and undifferentiated (4); no clear association of differentiation with mucin types was seen. Signet ring cell features (7) was associated with decreased $Lewis^x$ expression. Clear cell change (8) was not correlated with a particular mucin pattern. Two major patterns of intra-abdominal spread were noted: serosal studding (innumerable, minute foci of minimally invasive tumor) and carcinomatosis (diffuse large invasive tumor foci). Cases with serosal studding (10) had increased expression of MUCs 17, 6, 5AC, 7, and 4 (mild) when compared to carcinomatosis (6), in which the expression of MUCs 17, 7, and 6 was lost.

Conclusions: 1. Two distinct patterns of intra-abdominal spread of tumor were identified: serosal studding and carcinomatosis. These correlated with distinct mucin phenotypes.

2. Signet ring cell features correlate with a decrease in $Lewis^x$ expression.

3. No correlation with clear cell change or degree of differentiation was seen with mucin phenotype.

7 C4d: A Marker for Cardiac Allograft Vasculopathy

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Background: In the past decade C4d has emerged as a potential marker for antibody-mediated rejection (AMR); however, evidence on its use as a prognostic tool has been controversial. To date, there is no consensus of the value of C4d in the pathologic assessment of AMR. Here, we present a correlation of our prospective study of C4d immunoreactivity in endomyocardial biopsies with clinical cardiac dysfunction, cellular rejection, HLA status, death, and cardiac allograft vasculopathy (CAV) at autopsy.

Design: 3758 endomyocardial surveillance biopsies from 200 heart transplant recipients (1/2004 - 9/2010) were stained prospectively for C4d. Immunohistochemical stains were performed on paraffin-embedded tissue using an anti-human C4d polyclonal antibody. Strong diffuse endothelial staining was considered positive. All patients had at least 1 year of follow-up. Cardiac dysfunction at the time of positive biopsy was evaluated by echocardiography. Cellular rejection was graded per ISHLT 1990 criteria.

Results: Positive C4d staining was present in 43 biopsies from 25 patients (12%). 9/25 patients (36%) had clinically significant cardiac dysfunction at the time of positive biopsy. In C4d positive patients, the mean PRA was 33%. At first C4d positivity, concomitant cellular rejection was as follows: 15/25 (60%) grade 0, 3/25 (12%) grade 1A, 6/25 (24%) grade 1B, 1/25 (4%) grade 2 and 1/25 (4%) had grade 3B rejection. 24/200 patients (12%) died, 16 of whom (67%) were C4d positive. Autopsy was performed on 18 of the 24 deaths (8 C4d negative and 10 C4d positive patients). At autopsy 10/10 C4d positive patients had histologic evidence of cardiac allograft vasculopathy (CAV). Six of 8 C4d negative patients (75%) had no CAV, while 2/8 had CAV. Six C4d positive deaths did not have autopsy. Nine of 25 (36%) C4d positive patients are alive 1-3 years post-transplant.

Conclusions: C4d positive patients contributed to 67% of the overall mortality. All 10 autopsies (100%) on C4d positive patients revealed CAV as the cause of death. In the C4d negative group, 75% of all deaths were due to non-cardiac causes. These findings show a positive association of C4d with CAV and death. Our results indicate a prognostic role for C4d in heart transplantation warranting routine detection of this marker in the pathologic evaluation of cardiac AMR.

8 Do Patients Presenting with Atherosclerotic Heart Disease and Sudden Cardiac Death Have a Higher Body Mass Index?

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Background: A raised body mass index (BMI) has been associated with an increased risk of morbidity and mortality in atherosclerotic coronary heart disease (CHD) patients. We sought to identify an association between sudden cardiac death (SCD) in patients with atherosclerotic CHD and an increased BMI.

Design: A review of all SCD at the Hamilton General Hospital Forensics Unit, for the calendar year 2010, was performed. Clinical details including age, height, weight, symptoms prior to demise and histopathological details from the autopsy were collected. The body mass index was calculated in all cases. Standard statistical methods were used to determine if BMI was higher in patients with atherosclerotic CHD presenting with SCD. The control group for comparison included SCD patients without evidence of atherosclerotic CHD. Sub group analysis included comparison of BMI based on the sex of SCD patients.

Results: One hundred and ten (16.5%) of 666 autopsies conducted in 2010 were classified as SCD. Seventy-one (64.5%) cases of SCD were attributed to atherosclerotic CHD. Sudden cardiac death in the remaining patients was attributed to other causes. The results are summarized in Table 1 and Table 2.

Table 1

	SCD patients with atherosclerosis	SCD patients without atherosclerosis	P-value Paired t-test
Age in years (Mean ± SD)	59.86 ± 11.82	44.10 ± 13.74	<0.001 (HS)
BMI (Mean ± SD)	29.45 ± 7.49	28.37 ± 5.52	0.29 (NS)

Table 2

	Male SCD Patients with Atherosclerosis	Male SCD Patients without Atherosclerosis	P-value Paired t-test	Female SCD Patients with Atherosclerosis	Female SCD Patients without Atherosclerosis	P-value Paired t-test
Age in years (Mean ± SD)	59.70 ± 11.17	40.08 ± 12.91	<0.001 (HS)	60.23 ± 13.45	53.23 ± 11.11	0.078 (NS)
BMI (Mean ± SD)	28.50 ± 6.84	27.70 ± 4.62	0.45 (NS	31.60 ± 8.59	29.89 ± 7.12	0.44 (NS)

Conclusions: A significant difference was not noted in the BMI of SCD patients with and without atherosclerotic CHD. Analysis of BMI based on the sex of the patients also did not demonstrate a significant difference. Men presenting with SCD due to atherosclerotic CHD tended to be significantly older than those presenting with SCD due to other causes.

9 Acute Hepatic Hemorrhage in Hospital-Based Autopsy Series: A 21-Year Review

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Background: Acute hepatic hemorrhage can have a variety of causes. In this study, we reviewed the etiology and associated findings in hospital-based autopsy cases of liver hemorrhage.

Design: Retrospective search of subcapsular hematoma and liver laceration from a single medical center between 1990 and 2011 was performed. Fetuses and patients with liver transplantation or remote history of liver laceration were excluded.

Results: Thirteen cases of acute liver hemorrhage were found.

Causes of hepatic hemorrhage

Case	Age/Sex	Etiology for hepatic hemorrahge	Hemoperi-toneum	Diagnosis made antemortem	Cause of death	Clinical diagnosis
1	3/F	CPR	Yes	No	Transplant rejection	Dilated cardiomyopathy S/P transplant
2	9/M	CPR	Yes	No	Cerebral edema	Right temporal lobe cortical dysplasia
3	46/F	CPR	No	No	Pulmonary embolism	Uterine leiomyomas S/P hysterectomy
4	66/F	CPR	Yes	Yes	Sepsis	Aspiration pneumonia
5	69/F	CPR	Yes	No	Hemopericardium	Acute myocardial infarction
6	75/F	endoscopic retrograde cholangiopancreatography	No	Yes	Sepsis	Cholangio-carcinoma
7	58/F	portal vein stenting via transhepatic access	Yes	Yes	Massive hemoperitoneum	Pancreatic carcinoma
8	74/M	percutaneous transhepatic cholangiography	Yes	Yes	Carcinomatosis	Cholangiocar-cinoma
9	3/F	transcatheter closure of ventricular septal defect via transhepatic access	Yes	No	Massive hemoperitoneum	Pulmonary atresia with ventricular septal defect
10	29/F	spontaneous	Yes	No	Massive hemoperitoneum	Nephrolithiasis
11	67/F	spontaneous	No	Yes	Sepsis	Coronary artery disease
12	40/M	spontaneous	Yes	Yes	Massive hemoperitoneum	Ehlers-Danlos syndrome
13	73/F	trauma	Yes	Yes	Massive hemoperitoneum	Fall

There were 3 children and 10 adults with age ranging from 3 to 75 years. There was a female predominance (M:F ratio of 3:10). Nine cases were iatrogenic (64%), 3 cases were spontaneous (23%), and 1 case was traumatic (8%). Of the 9 iatrogenic cases, 5 were due to cardiopulmonary resuscitation (CPR) and 4 cases occurred after procedures related to the hepatobiliary system. Eight cases involved the right lobe, 4 cases involved the left lobe and 1 case involved both lobes. Three cases showed subcapsular hematoma that did not rupture. Ten cases were associated with hemoperitoneum which was the immediate cause of death in 5 patients. The clinical team was not aware of the hepatic hemorrhage prior to autopsy in 2 of the 5 cases with massive hemoperitoneum.

Conclusions: The occurrence of hepatic hemorrhage is extremely rare but can have grave consequences, particularly when it results in massive hemoperitoneum. Most cases of liver injury in the hospital setting were iatrogenic in nature.

10 Isolated Right Ventricular Myocardial Infarction

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Background: Isolated acute right ventricular myocardial infarctions (RVMI) are not well characterized. The right ventricle is less susceptible to ischemia, but several factors can increase oxygen demand or decrease oxygen supply, and predispose the right ventricle to ischemic damage. The incidence of isolated acute RVMI may be underestimated due to lack of detection. Tetrazolium staining is useful in the detection of early myocardial ischemia, but it is often not routinely used in the autopsy setting. The purpose of this study was to investigate the cardiac and associated findings of isolated acute RVMI and the utility of tetrazolium staining to detect myocardial ischemia in this setting.

Design: We retrospectively searched all adult autopsy cases over a 60-month period for isolated acute RVMI. Pathologic evidence of myocardial ischemia was defined by gross examination after incubation with nitroblue tetrazolium solution and by microscopic evidence of neutrophil margination, contraction band necrosis or coagulation necrosis.

Results: Thirteen cases of isolated acute RVMI were identified comprising 0.7% of all autopsies in the study period. There were 5 males and 13 females with age ranging from 43-86 years. Eleven patients had cardiomegaly (85%) with right ventricular dilation in 8 cases. The thickness of the right ventricle was ≥0.5 cm in 6 cases (46%). Ten cases had right dominant coronary circulation, one case had co-dominant circulation, and two cases had undescribed circulation. Right coronary circulation pathology included significant coronary artery disease defined as ≥ 75% luminal stenosis in 4 patients, hypoplastic right coronary artery in 1 patient and small vessel disease in another patient. Three patients had clinical evidence of pulmonary hypertension. The lungs demonstrated hypertensive vasculopathy in 4 patients and pulmonary thromboembolism in 4 cases. Tetrazolium staining was performed in 10 cases and identified areas of myocardial ischemia in all cases that were confirmed on microscopy. Ischemia involved the entire free wall in 10 cases, the posterior wall in 2 cases, and the anterior wall in 1 case. The cause of death was determined directly related to RVMI in 10 cases, while 2 patients died of massive pulmonary embolism and one patient died of respiratory failure.

Conclusions: Right coronary artery disease and pulmonary hypertension are risk factors for developing isolated acute RVMI. This study shows that tetrazolium staining is a useful and sensitive method to look for evidence of early acute ischemic changes.

11 Pulmonary Hypertension in Adult Sickle Cell Patients at Autopsy

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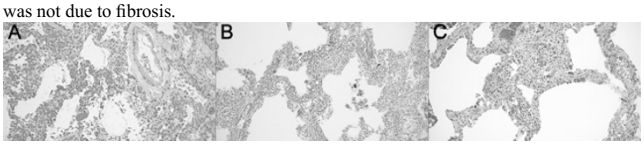
Background: Pulmonary hypertension (PH) in patients with sickle cell disease (SCD) has a poor prognosis. Previous autopsy studies have reported up to 100% of SCD patients with muscular hypertrophy and intimal fibrosis, 60% with plexiform lesions and 50-75% with chronic thromboembolic disease. However, clinically less than a third of SCD patients have PH, and half of these have pulmonary venous hypertension (PVH) due to left ventricular diastolic dysfunction. Given the discrepancy in the severity of histological and clinical findings, we examined a larger series of SCD autopsies.

Design: This was a retrospective analysis of adult SCD patients autopsied at our institution since 1993. Patients were included if hemoglobin electrophoresis confirmed SCD or if there was a history of complications from SCD. Autopsy reports, all lung slides and elastic, trichrome, reticulin and iron stains on one section were examined from each case.

Results: Plexiform lesions were entirely absent in all 19 patients. Five patients had no vascular changes and 4 had only rare recanalized small arteries. Of the remaining 10 patients, 6 had recanalization of large (>1mm) vessels and 6 had frequent recanalization of smaller arteries. Variable degrees of intimal fibrosis and/or muscular hypertrophy were present in only 7 cases (37%). In addition, 3 patients (16%), all with evidence of chronic thromboembolic disease, had extensive thickening of the alveolar walls due to increased capillary vessels (Fig 1A). Reticulin stain (Fig 1B) confirmed increased capillaries in individual alveolar septa rather than congestion and atelectasis. Unlike pulmonary capillary hemangiomatosis (PCH) however, no capillary invasion of bronchi or blood vessels was present. Trichrome stain (Fig 1C) confirmed that wall thickening was not due to fibrosis.



Signs of PVH, including arterialization of veins or iron-encrusted elastic fibers were absent in all cases. None of the findings correlated with right ventricular hypertrophy.

Conclusions: Morphologic findings of PH in SCD were less frequent and less severe than previously reported. This is the first report of PCH-like changes in SCD, which have been previously described in association with pulmonary veno-occlusive disease and left heart failure, neither or which could be morphologically diagnosed in our cohort.

12 A Novel Challenging Role for Pathologists: Direct Verbal Communication of Autopsy Findings to Families in a Risk Management Program

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Background: Research indicates that effective communication following unexpected harm is essential to maintaining patient and family trust. Within the federally funded patient safety program at the University of Illinois Medical Center at Chicago (UIMCC) pathologists have become uniquely involved in UIMCC's comprehensive communication process following patient harm events. The objective of this research was to identify key competencies required of pathologists to function successfully in such a multidisciplinary program.

Design: The safety and risk management team facilitates interdisciplinary communication with patients and families following all serious harm, including death. The team assesses the effectiveness of these communications and tracks claims data. Members of the interdisciplinary team reviewed data related to participation of autopsy pathologists in the program and identified quantitative and qualitative outcomes, as well as key desired competencies.

Results: From 2006-2008, risk management facilitated 127 patient/family communication consultations. A UIMCC pathologist participated in five and of these an autopsy was performed in four. When a pathologist was involved, their competency in the process was assessed favorably by risk management and rated positively by the family members. None of the cases that involved a pathologist resulted in a claim. The consensus of the interdisciplinary team was that in addition to medical knowledge, the most important competencies for pathologists to successfully participate in the process are compassion, empathy, and the ability to establish patient trust.

Conclusions: Following harm, effective communication processes allows the multidisciplinary team to learn and improve. The pathologist can play a pivotal role as part of a multidisciplinary team in providing objective data while answering questions to help families understand the cause[s] of death, thereby, eliminating the need to pursue litigation to get questions answered. Successful participation in these increasingly prevalent programs requires pathologist to use skills not traditionally central to pathology practice and pathology training programs. These experiences will lead to the increased recognition of the importance of autopsies by clinicians and underline the indispensible role of autopsies in risk management programs.

13 Postmortem Evaluation of Kidney and Other End-Organ Toxicity in Glioblastoma Patients Treated with Bevacizumab

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Background: Bevacizumab (BEV) alone or in combination with temozolomide (TMZ) and/or irinotecan is the main chemotherapy option for progressive glioblastoma (GBM). BEV containing regimens are also widely used for metastatic kidney, breast, colon and lung cancers. There are concerns of permanent organ damage from long term use of BEV containing regimens. However, post-mortem examination of end-organ toxicity has not been reported.

Design: Postmortem organ specific morphologic studies including electron microscopy (EM) and immunofluorescence (IF) were performed in 10 cases of progressive GBM treated with TMZ and BEV containing regimens. 9 male and 1 female subjects were included, ranging from 50 to 77 years of age (median 57 years old). All subjects were treated at Tufts Medical Center, Boston and received palliative care prior to their death. All patients initially received standard treatment for GBM with subsequent monthly TMZ. After GBM progression they received BEV every the other week at 10 mg/kg with TMZ or irinotecan (5-49 treatments, median 17 treatments). Medical records of all 10 subjects were reviewed. Clinical toxicities and laboratory abnormalities were documented. Institutional review board (IRB) clearance and autopsy consents form the next of kin were obtained.
Results: The cause of death in most patients was bronchopneumonia (8/10). Clinically, apart from symptoms related to tumor progression in relevant cases, 8 subjects receiving BEV treatment developed proteinuria (trace to 3+) and 4 subjects developed hypertension. In 9 out of 10 unlimited autopsies (one was brain and kidney only). There was no significant morphologic evidence of TMZ/BEV-related injury in heart, liver, adrenal glands, thyroid, pancreas, spleen, or bone marrow. In all subjects the glomeruli revealed diffuse variable degree of glomerular basement membrane thickening with segmental to global double contours and without proliferative lesions. EM examination of the kidneys showed homogenized substructure and subendothelial rarefaction with some wrinkling of the glomerular basement membrane. The vasculature showed variable mural thickening as observed in hypertensive changes. IF examination showed no immune complex depositions.
Conclusions: With the exception of the kidneys, there appears to be no significant end-organ damage associated with treatment with TMZ and BEV of variable durations. Renal toxicity manifests as mild-to-moderate endothelial damage which was clinically associated with variable proteinuria and hypertension.

14 Utility of Rapid Cytologic Techniques in the Autopsy Setting

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Background: Interest in the autopsy may be augmented by providing families and clinicians with more timely results. Rapid cytologic techniques employed during the prosection may provide quick and accurate pathologic diagnoses as well as maximize the educational experience in an academic hospital setting. Few publications have addressed the utility of cytologic techniques as an immediate diagnostic tool in the autopsy setting.
Design: Over a 2 month period of time at a tertiary care academic hospital, rapid cytologic diagnostic techniques were applied to 41 consecutive autopsy cases when focal lesions were present (24 male, 17 female, age range 31-100 years). Air-dried touch preparation, smear, and fine needle aspiration slides were stained with a Hemacolor rapid stain, and evaluated during the prosection by a cytology fellow with cytology attending consultation. Results were included in preliminary autopsy diagnoses and correlated with final histologic outcomes.
Results: Focal lesions amenable to cytologic sampling were present in 49% (20/41) of all autopsy cases over this time period. Of these, 15% (3/20) represented the primary tissue diagnosis of previously unknown malignancy, 50% (10/20) confirmed metastatic foci of a known primary tumor, 15% (3/20) identified fungal/bacterial infectious processes, and 5% (1/20) identified benign reactive processes. Mononuclear cell populations without discernible microorganisms were found in 10% (2/20) of cases, subsequently shown on histology to be fungal in nature. Non-diagnostic findings were present in one case, a lung nodule which on histology was proven to be a reactive pneumocyte process.
Conclusions: The application of rapid cytologic techniques to selected autopsy cases with focal lesions is a quick, simple, and low-cost adjunct to gross findings which provided important diagnostic information in 95% of cases. The cytologic material in this study provided good overall cytomorphology, and in a number of cases directed the prosector's dissection and established the first pathologic diagnosis of malignancy. Inclusion of cytologic diagnoses was well received by clinicians attending autopsy conference, and provided more immediate and definitive pathologic diagnoses to clinical questions which were included in the preliminary autopsy diagnosis. From an educational standpoint, this approach helped familiarize junior residents to the evaluation of cytologic specimens, provided subsequent cytologic-histologic correlation, and improved the quality of the autopsy experience.

15 Transthyretin Amyloidosis: The Heart and beyond

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Background: The most common mutation leading to cardiac amyloidosis in the US is the V122I mutation, present in 3-4% of African-Americans. We studied the distribution of TTR amyloid deposition in autopsy material from our predominantly African-American patient population in order to better characterize the pathology associated with the V122I mutation. Since an association of wild-type TTR deposition in systemic senile amyloidosis (SSA) and myocardial infarction has been reported in a Finnish population, we also assessed whether any myocardial infarcts were present.
Design: Cases of TTR cardiac amyloidosis and age-matched controls were identified from 2007-2010 autopsy records. The presence of amyloid deposition in tissues was examined by H&E, Congo Red, and TTR immunohistochemistry. Apoptosis was measured by TUNEL staining.
Results: Four cases of TTR cardiac amyloidosis (average age 82.8 years; range 80 to 87 years) were identified. TTR gene sequencing identified mutant TTR (V122I) in three cases and wild-type (WT) TTR in one case. No myocardial infarcts were identified in cases or controls, however, there was an increase in apoptosis in the myocardium in the TTR cases compared to controls. Cardiac amyloidosis was in a patchy and diffuse distribution in the sub-endocardium, sub-epicardium, and myocardium in all the cases and in pericardial adipose tissue in two of three V122I cases. Amyloid was not present in the major coronary arteries but was found in smaller epicardial vessels in all of the cases. In addition to the heart, amyloid deposition was present variably in blood vessels of multiple tissues including adrenal gland, appendix, bladder, colon, esophagus, gallbladder, kidney, liver, lung, pancreas, prostate, spleen, stomach, thyroid, tongue, adipose, pancreas and kidney. Interstitial deposition of amyloid was also seen in the adrenal gland (1 V122I), bladder (1 V122I), gallbladder, esophagus (1 V122I case), colon (2 V122I), liver (1 WT and 1 V122I case), prostate (1 V122I case), kidney (1 WT and 2 V122I), and spleen (1 V122I case).
Conclusions: Although the heart was the most severely affected organ, TTR amyloid deposition extended beyond the heart in all four cases with the distribution varying among the individual cases. Frequent involvement of coronary arteries with amyloid has been reported in cases of AL amyloidosis, however, no TTR amyloid deposits were seen in the major coronary arteries in the four cases studied. Unlike SSA amyloidosis in the Finnish population, no myocardial infarcts were identified.

16 The Histopathology of the Liver in HIV+ and Acquired Immunodeficiency Deficiency Syndrome (AIDS) Individuals in the HAART Era

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Background: Histopathological changes in the liver of AIDS patients have not been well documented in the HAART era. With longer survival, patients are now developing more advanced and varied liver disease without the opportunistic infections that they once had. Recently, an association between didanosine and non-cirrhotic portal hypertension (NCPH) due to either nodular regenerative hyperplasia (NRH) or hepatoportal sclerosis (HPS) in HIV patients has been described.
Design: Since 1999, our institution has accrued over 250 HIV+/AIDS autopsy cases via an NIH-funded Manhattan Brain Bank database. These individuals volunteer to donate their organs at post-mortem. From this cohort, we selected 77 archival liver autopsy specimens that were available for review and performed a detailed clinicopathological analysis. Grade and stage for chronic hepatitis was based on Batts and Ludwig scheme and grade and stage for steatohepatitis was based on the Brunt classification. Hepatoportal sclerosis was noted when there was phlebosclerosis and concurrent signs of portal hypertension such as splenomegaly were present.
Results: There were 40 males and 37 females; average age was 49 years (range = 20-84). Mean HIV infection duration was 11.7 years (range = 2 months-20 years). Six patients had recent (< 1 year) of HAART treatment. CD4 counts were documented for 39 patients: 14 with 0-100, 19 with 100-399, and 6 more than 400 CD4+ cells. Twenty-seven of 77 (35%) were (+) for viral hepatitis (19 HCV; 7 HCV+HBV; 1 HBV). Cirrhosis was seen in 15/27 (55%); 8 (30%) had NCPH (3NRH, 5 HPS); 4 (15%) had steatohepatitis. Only 1 of 8 patients with NCPH and positive viral hepatitis was taking HAART at the time of death. Of the 50 cases with negative viral hepatitis, 15/50 (30%) had cirrhosis; 19/50 (38%) had cryptogenic chronic hepatitis with fibrosis ranging from mild to advanced fibrosis; 11/50 (22%) had NCPH; 5/50 (10%) had steatohepatitis.
Conclusions: This study documents that significant liver disease occurs in HIV/AIDS. Our series shows that the incidence of noncirrhotic portal hypertension is high in this patient population and that chronic idiopathic hepatitis in the absence of HCV or HBV infection, and alcohol use is common. The etiology of this hepatitis remains to be elucidated. Patient involved in this study may have taken pre-HAART era medications such as didanosine, but was not documented.

17 DSG2 Mutations in ARVC: A Molecular Autopsy Study

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease of the cardiac muscle that causes severe arrhythmias and sudden death. It has been linked to mutations in several desmosmal related proteins including plakophilin-2 (most prevalent), desmoglein-2, (DSG2), desmocollin-2, desmoplakin, and plakoglobin. Clinical series of ARVC patients report mutations of any type in approximately 50% of patients, and DSG2 mutations in approximately 10% of patients. However, the diagnosis of ARVC is clinically variable and can be challenging in living patients. In this study, to determine the role of DSG2 mutations in ARVC, we sequenced DSG2 in autopsy cases with definitive histologic diagnoses of ARVC.
Design: DNA was extracted from the post-mortem tissues of 25 patients dying suddenly with ARVC, and the 15 exons of DSG2 were sequenced. The primers were designed using Primer Express 3.0 software. Direct sequencing for both sense and antisense strands was performed with a BigDye Terminator DNA sequencing kit on a 3130 Genetic Analyzer with SeqScape software.
Results: DSG2 mutations were identified in 2 of 25 ARVC patients, both of which were novel. One of the mutations (3075_3076 ins C) is an insertion in exon 15 and is considered to be damaging, while the other (2092G>A), a missense mutation in exon 14, was determined to be 'possibly damaging' by PolyPhen and 'benign' by Mutation Taster and SIFT software.
Conclusions: There have been few molecular autopsy series of ARVC patients that looked for mutations in desmosomal related proteins. Here we report two novel DSG2 mutations in patients dying suddenly with histologically diagnosed ARVC. In this small autopsy series, we observed a DSG2 mutation prevalence of 8% in ARVC patients, which corresponds to the approximately 10% seen in clinical ARVC series. This study establishes the usefulness of molecular autopsy studies in patients with sudden death.