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205 Dual Duodenal ApoAIV Amyloidosis and Cardiac ATTR Amyloidosis Arising in the Same Patient: A Distinct Clinicopathologic Entity?

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Disclosures: Linda Dao: None; Surendra Dasari: None; April Chiu: None; Karen Rech: None; Martha Grogan: *Primary Investigator*, Alnylam, Eidos, Prothena, Pfizer; Melanie Bois: None; Catherine Hagen: None; Ellen McPhail: None

Background: ApoAIV (Apolipoprotein A-IV) amyloidosis is an uncommon amyloid type that primarily involves heart, kidney and gastrointestinal tract. ATTR (transthyretin-type) amyloidosis is a common cause of cardiac amyloidosis, although it may involve nearly any organ system. Although uncommon, patients with two different amyloid types in two different anatomic sites have been previously described. Since amyloid therapies vary dramatically depending on the specific precursor protein, accurate typing of amyloid deposits is crucial for optimal patient care. We became aware of an index case of a patient with duodenal ApoAIV amyloidosis and cardiac ATTR amyloidosis, which prompted this study.

Design: We queried our reference laboratory database of 19,298 internal and external amyloid specimens from myriad anatomic sites typed by mass spectrometry-based proteomics (LC-MS/MS) for patients with dual diagnoses of ApoAIV and ATTR amyloidosis. Demographic data including patient age, sex, and anatomic site of involvement was abstracted in all cases, and pertinent clinical information was reviewed when available. H&E and Congo red-stained slides as well as the mass spectrometry proteomic features were reviewed.

Results: We identified three patients with dual diagnoses of ApoAIV and ATTR amyloidosis. All three were men and the age at initial diagnosis was 71, 78 and 82 years. In all three cases, there was duodenal involvement by ApoAIV amyloidosis and myocardial involvement by ATTR amyloidosis. All ATTR amyloidosis specimens were negative for mutant peptides indicative of a pathogenic ATTR mutation, and this result was confirmed by Sanger sequencing in one case. One patient had undergone technetium-labelled cardiac scintigraphy, which was positive, but was assumed to be a false-positive result until the mass spectrometry results were obtained.

Conclusions: The findings raise the possibility of a distinct clinicopathologic entity characterized by duodenal involvement by ApoAIV amyloidosis coupled with myocardial involvement by ATTR amyloidosis. Further study of additional cases is needed to understand this phenomenon better. These results underscore the importance of determining the amyloid type in all cases, preferably by the gold-standard method of mass spectrometry-based proteomics, and demonstrate that at least in some cases, typing of more than one anatomic site is required for optimal patient care.

206 Diagnosing Myocarditis in Endomyocardial Biopsies: Survey of Current Practice

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Background: Dallas criteria (DC) and European Society of Cardiology (ESC) criteria have provided valuable frameworks for the histologic diagnosis and classification of myocarditis in endomyocardial biopsy (EMB) specimens. However, the adaptation and usage of these criteria is variable and depends on local practice settings. Moreover, several ancillary tests that are not included in the current criteria such as immunohistochemistry (IHC) or viral PCR, have proven useful for the diagnosis of myocarditis.

Design: As a joint effort from the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP), we conducted an online survey to understand the current practice of diagnosing myocarditis.

Results: A total of 100 pathologists from 23 countries responded to the survey with the majority practicing in North America (46%) and Europe (43%). Most of the pathologists (85%) examined less than 200 native heart biopsies per year, and rendered diagnosis of myocarditis less than 30 cases per year (92%). Most of the pathology labs (89%) routinely receive 3-5 fragments of tissue per case. The number of hematoxylin-eosin stained levels for each case varies from 1 to more than 9 levels, with 20% of pathologists routinely asking for more than 9 levels per case. Among the 100 pathologists, 80 use DC and 41 the ESC criteria. Breaking down by regions, DC is more commonly used than ESC criteria in North America (80% versus 19.6%) while both criteria are commonly

used in Europe (79.1% and 62.8%). IHC is utilized in either every case or selected cases for 79% of participants, and viral PCR is performed by 32% of participants. Variable terminologies are used in EMB myocarditis reporting, some as histological diagnoses and others as clinical diagnoses (e.g. fulminant myocarditis), and 34 pathologists do not use the term “borderline myocarditis”. The majority of the participants think it is time to update the current criteria (83%).

Conclusions: The survey data demonstrated that pathologists who diagnose myocarditis practice with variable tissue preparation, ancillary studies, guideline usage and reporting. These results highlight the clinically unmet need and desire to update and standardize the current diagnostic criteria for myocarditis on EMB. Additional studies are warranted to establish standard of practice.

207 Clinicopathological Correlations in Patients Undergoing Endomyocardial Biopsy for Clinical Suspicion of Myocarditis

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Background: Myocarditis is an inflammatory disease of the heart muscle caused by infections, exposure to toxic substances, or immune system activation. Endomyocardial biopsy (EMB) is the gold standard for diagnosis.

Design: We correlated morphologic findings with clinical presentation in 100 patients consecutively referred to our Institution with clinical suspicion of myocarditis from 1st January 2009 to 31st December 2020. Histologic diagnosis was based on Dallas Criteria combined with immunohistochemical analysis and molecular studies (PCR) according to the European Society of Cardiology position statement (2013).

Results: Myocarditis was confirmed by histology in 23/100 patients (23%) who were diagnosed with lymphocytic myocarditis (17/23, 74%), giant cell myocarditis (3/23, 13%), toxic (catecholamine) myocarditis (2/23, 9%), and cardiac sarcoidosis (1/23,4%). Patients presented clinically with acute or subacute heart failure (15/23, 65%), rhythm disturbances (22%) or both (13%). Two out of three patients with giant cell myocarditis presented with cardiogenic shock requiring mechanical circulation support (i.e. fulminant myocarditis).

Viral genomes (Parvovirus B19 and EBV) were identified in 2/20 patients (10%). One patient reported familiarity for immune-mediated disease.

Of the 77/100 (77%) patients in whom the clinical suspicion of myocarditis was not confirmed by histology, 64/77 (83%) showed mild to severe cardiomyopathic features (i.e. cardiac myocytes hypertrophy and cytoplasmic vacuolization) associated with myocardial scarring (32/64; 50%) and moderate interstitial edema (21/64; 33%). Interestingly, 19/64 cases (30%) showed remodeling of coronary arterioles with medial wall thickening. Most of the patients presented clinically with chronic heart failure (23/64, 50%), rhythm disturbances (22%) and acute chest pain (32%). The latter was evident in 10/19 (53%) patients with remodeling of coronary arterioles.

Viral genomes were identified in the myocardium of 6/64 patients (10%). Familiarity for immune-mediated disease was evident in 26/64 (41%) patients and, interestingly, in 12/19 (63%) of those with microvascular remodeling.

Conclusions: Sensitivity of EMB in confirming the diagnosis of myocarditis is higher in patients with acute presentation. Within a specific clinical setting cardiomyopathic features associated with interstitial edema and fibrosis may suggest a chronic inflammatory cardiomyopathy. Microvascular remodeling may underlie immune-mediated damage.

208 Aortic Valve Amyloid Predicts Myocardial Amyloid Deposition

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Disclosures: Philip Hurst: None; Ellen McPhail: None; Surendra Dasari: None; Marie-Christine Aubry: None; Peter Lin: None; Ying-Chun Lo: *Advisory Board Member*, Takeda Pharmaceutical Company Limited; Shareef Mansour: None; Martha Grogan: *Primary Investigator*, Alnylam, Eidos, Prothena, Pfizer; Omar AbouEzzeddine: *Grant or Research Support*, Pfizer, Inc.; Joseph Maleszewski: *Consultant*, Edwards Scientific; Melanie Bois: None

Background: Aortic valve (AV) amyloid is common, reportedly occurring in 15-82% of surgically resected valves. At our institution, 52% of surgically resected AVs contained amyloid with two distinct morphologies, one occurring adjacent to calcium deposits (calcific) and the other occur away from such (extracalcific). The degree to which these morphologic types correlate with myocardial amyloid is not yet established.

Design: Autopsy archives were queried for cases of ATTR (transthyretin)-type cardiac amyloidosis (CA) and cross-referenced with antemortem aortic stenosis (AS) (2013-2020). Patients (pts) were separated into three groups: CA with AS, CA without AS, and AS without CA. Salient clinical information was abstracted from the medical record. AVs were dissected from stored tissue, paraffin-embedded, and stained with Congo red (CR). Mass spectometry-based proteomics (LC-MS/MS) was used to characterize CR(+) deposits on a subset of AVs and myocardium (where applicable).

Results: 5 cases of CA with AS, 9 cases of CA without AS, and 4 cases of AS without CA were identified, with AV amyloid frequency of 4 (80%; 2 extracalcific, 1 calcific, 1 mixed), 6 (67%; all extracalcific), and 1 (25%; mixed), respectively. Upon review, CA was identified in the single case of AS without CA (previously missed). 5 cases (3 extracalcific, 2 mixed pattern) underwent LC-MS/MS. All purely extracalcific deposition cases typed as ATTR amyloid. Extracalcific foci in the mixed pattern cases typed as ATTR amyloid, while the calcific foci had proteomic features of amyloid but a definitive amyloid type could not be established. All AVs with extracalcific amyloid showed myocardial deposition of ATTR amyloid.

Conclusions: Amyloid deposition in AVs is common; however, in this limited series, only the extracalcific variety appears to reliably correlate with ATTR CA. Analysis of additional cases is ongoing as this finding suggests immediate clinical import of this histologic pattern. The significance of calcific amyloid is still uncertain, requiring further study both in terms of its role in aortic stenosis and its association with cardiac and/or systemic amyloidosis.

209 Somatostatin Receptor Expression in Cardiac Hemangiomas

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Disclosures: Andrew Layman: None; Melanie Bois: None; Phillip Young: None; Joseph Maleszewski: *Consultant*, Edwards Scientific

Background: Cardiac hemangiomas are an uncommon benign cardiac tumor with management depending largely on clinical symptomatology. Cardiac paragangliomas, in contrast, may secrete catecholamines and be locally invasive, leading to surgical resection as a mainstay of treatment. Thus, accurate pre-operative diagnosis is essential and accomplished primarily through somatostatin receptor analogs and ^{68}Ga-DOTATATE-positive imaging in the latter. However, a recent case of surgically resected ^{68}Ga-DOTATATE-positive cardiac hemangiomas was discovered. We sought to characterize somatostatin receptor (SSTR) expression in cardiac hemangiomas.

Design: Tissue archives were reviewed for cases of cardiac hemangiomas from 1997-2021. Formalin-fixed, paraffin embedded tissue for each case was sectioned at 4 microns and stained with hematoxylin and eosin (H&E) and subsequently stained for somatostatin receptor (SSTR2, clone UMB1; Abcam) by immunohistochemistry. A SSTR2 H-score was calculated for each case through the product of the stain intensity (0-3) and the stain distribution among tumor cells (0, 1:<25, 2: 25-75, 3:>75). Macrophages were identified with CD68 (KP1; Dako) to exclude activated histiocytic uptake.

Results: 5 cases of cardiac hemangioma were identified (mean patient age, 50.4 years (range 35-75); 3 women). The tumors occurred were both intramural and epicardial in origin; 3 were right ventricular, one right atrial, and one involved the mitral valve. The morphologic subtypes included cavernous (n=1), capillary (n=3), and mixed (n=1). The preoperative clinical and

radiographic impressions included: sarcoma, arteriovenous malformation, hamartoma, and paraganglioma. One case underwent DOTATATE-imaging, showing a SUV max of 6.9 which was suspicious for a paraganglioma.

The average H-score among all tumors was 5.8 (range, 2-9). Capillary subtypes showed more diffuse staining, attributed to the increased cellularity of the lesion. One case was a capillary type that showed a low H-score (2). Macrophage staining was low in all tumors reviewed.

Conclusions: Cardiac hemangiomas show variable but meaningful expression of SSTR, causing increased uptake on nuclear ^{68}Ga-DOTATATE scans. This finding expands the radiologic differential for lesions with such uptake. The finding may also offer additional insights for our understanding of the pathobiology of these unusual tumors.

210 Rabbit-Derived Anti-thymocyte Globulin Treated Transplant Heart Biopsies Have a Distinct Phenotype on C4d Immunofluorescence That Does Not Mimic Antibody Mediated Rejection

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Disclosures: Alexander McGeough: None; Jennifer Cook: None; Divya Sharma: None

Background: Anti-thymocyte globulin (ATG) induction therapy is associated with lower incidence of rejection and improved overall survival in heart transplant recipients. Horse derived-ATG is associated with C4d deposition in endomyocardial biopsies (EMB) in adult transplant recipients. Rabbit-derived ATG has been found to have a similar effect in the pediatric population; and the effect of rabbit-derived ATG on the adult cardiac transplant population has yet to be described. We investigate the association of rabbit-derived ATG and C4d deposition within the adult heart transplant recipients and study its pattern of deposition on immunofluorescent examination.

Design: UCMC results of C4d immunofluorescence were available from EMB of adult patients who received rabbit-derived ATG induction therapy between 2017-9/2021 (n=10). Electronic medical records were analyzed to identify if they had a diagnosis of AMR. Saved images of IF examination were reviewed to identify the pattern of C4d deposition.

Results: C4d expression was detected in 6/10 (60%) biopsies, and no patients were diagnosed with clinical or pathologic AMR. Immunofluorescence (IF) images were available for evaluation in these 6 patients and all of them (100%) had C4d deposition in a diffuse speckled pattern with intensity ranging from 1+to 2+, interpreted as negative for AMR.

Figure 1: Image of the diffuse and intense interstitial staining phenotype secondary to ATG therapy (top) and IF from a patient with AMR (bottom). The distinction between the two is readily apparent.

Figure 1 - 210

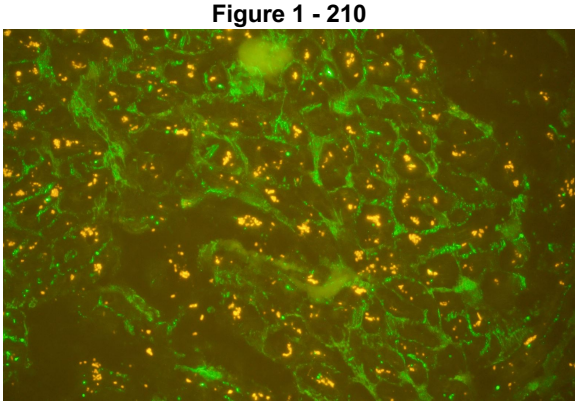
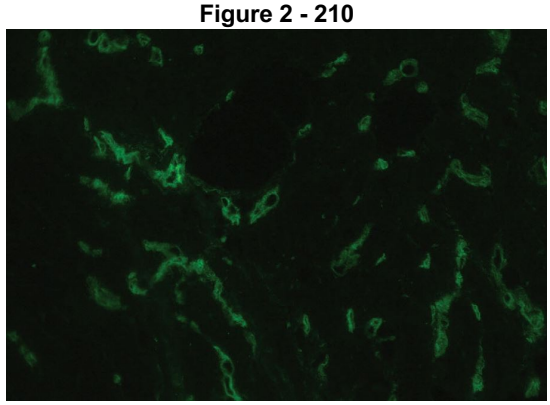


Figure 2 - 210



Conclusions: Our study shows that the incidence of C4d deposition in EMB of adult population post rabbit-ATG therapy (6/10; 60%) is similar to what has been reported in the pediatric population (approximately 50% in early post-transplant period). When C4d deposits are present, they show a diffuse, speckled, 1+ to 2+ intensity pattern of staining which is distinct and not to be confused with the capillary distribution or ‘donut’ pattern of AMR.

211 Radiologic and Pathologic Correlation Among Myocarditis and Infiltrative Cardiomyopathies on Endomyocardial Biopsy: An Institutional Experience

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Disclosures: Alexander McGeough: None; Catherine Taylor: None; Lauren Rosen: None; Divya Sharma: None

Background: Infiltrative Cardiomyopathies comprise heterogenous group of disorders including sarcoidosis, amyloidosis, hemochromatosis etc. which result in restrictive cardiac physiology. Inflammatory myocarditis includes lymphocytic, lympho-histiocytic and eosinophilic myocarditis. Advances in non-invasive cardiovascular imaging such as cardiac magnetic resonance imaging(CMR), echocardiography(ECHO), and positron emission tomography(PET) have improved diagnosis of inflammatory/infiltrative heart disease. Sensitivity and positive predictive value (PPV) of these techniques range from 76%-100% and 57-99% respectively. We aim to correlate imaging and histologic findings in native heart biopsies and compare our experience with that reported in literature.

Design: All native heart endomyocardial biopsies (n=25)received at our institute from 2017 to 2021 based on imaging suspicion for inflammatory/infiltrative heart disease were included in the study. The data was analyzed to determine the sensitivity and positive predictive value of imaging based on the final pathologic diagnosis.

Results: Imaging modalities included CMR(19/25,76%), ECHO(5/25,20%), and PET (1/25, 4%). Inflammatory/infiltrative findings on biopsy were present in 11/25 (44%) cases (myocarditis 64% [7/11]; amyloid 18% [2/11]; fatty infiltration 9%[1/11] and mitochondrial cardiomyopathy 9% [1/11]). 14/25(56%) cases with positive imaging, had no histologic evidence of inflammation, sarcoidosis or amyloidosis. Overall sensitivity of imaging was found to be 100% (11/11), however, the positive predictive value was 44% (11/25). All false positive (14/25; 56%) on imaging for inflammatory/infiltrative cardiomyopathy showed interstitial fibrosis(14/14;100%).

Conclusions: Imaging modalities are highly sensitive(100%) in diagnosis of inflammatory/infiltrative cardiomyopathies. However, positive imaging results need to be interpreted with caution due to significant false positives (56%) and a low PPV (44%) which may reflect low prevalence of this subset of cardiac diseases. All false positive biopsies in our study had interstitial fibrosis which were interpreted as inflammatory/infiltrative disease by highly sensitive imaging modalities. More studies are required to confirm this finding.

212 Inflammatory Features of Fatal Thrombosed Coronary Plaques in Cases of Sudden Cardiac Death: Post-mortem CT Angiography and Pathology Correlations

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Disclosures: Katarzyna Michaud: None; Virginie Magnin: None; Allard Van Der Wal: None; Silke Grabherr: None; Salah Qanadli: None; David Rotzinger: None

Background: Atherosclerotic coronary artery disease is the most frequent cause of sudden cardiac death (SCD). Postmortem imaging by means of multi-phase post-mortem CT angiography (MPMCTA) enables, apart from detection of coronary artery luminal occlusions, evaluation of the feature 'atherosclerotic plaque enhancement'. This has been postulated to be a marker of inflammation in carotid artery plaques but never been evaluated in postmortem imaging of coronary arteries. The goal of this study was to validate the concept of 'plaque enhancement' by comparing histological findings of plaque and periadventitial inflammation with MPMCTA characteristics of plaque enhancement in fatally thrombosed coronary plaques retrieved from SCD cases at autopsy.

Design: Fifty cases with autopsy-proven fatal coronary thrombosis were selected, of which the histological slides of coronary arteries were available and in which radiological examination by MPMCTA was performed. Eighteen were excluded due to histological or radiological artifacts. Thirty-two cases were included in the analysis (twelve women, 38%; median age 52 y, IQR; 8.75y). Haematoxylin and Eosin stained sections were assessed by two forensic pathologists in consensus for thrombotic occlusion and plaque composition, including intraplaque- and periadventital inflammation as well the density of vasa vasorum.

Parameters were all evaluated semi-quantitatively. CT images were assessed as presence or absence of plaque enhancement by two radiologists in consensus.

Results: Twenty cases showed a clear sign of radiological plaque enhancement at MPMCTA and twelve were negative. Histology confirmed acute atherothrombotic occlusion. Significant intraplaque inflammation (n=22), perivascular inflammation (n=19) and increased vasa vasorum (n=27) resulted in predictive positive value of 95% and negative predictive value of 25%. Radiology/histology correlation showed *p* values of 0.02 for intraplaque inflammation, 0.19 for adventitial inflammation and 0.01for vasa vasorum.

Conclusions: Post-mortem CT angiography plaque enhancement correlates with histopathological presence of plaque inflammation and increased vasa vasorum, which could support the postmortem detection of inflamed acute atherothrombotic coronary occlusions. Our post-mortem findings open the door to further validation studies and hopefully translation to clinical use.

213 Histopathological Evaluation of Type A Aortic Dissection: A Comparison of Congenital versus Acquired Aortic Wall Weakness

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Background: Aortic dissection is a catastrophic event associated with high mortality. However, its comprehensive pathogenesis is not well understood. We aim to study the aortic wall histopathology in Type A dissection patients with congenital versus acquired aortic wall weakness.

Design: Retrospective chart review of patients who underwent Type A dissection repair in 2019 was done. 34 patients (26 men and 8 women) were retrieved. Patients were divided into 2 groups, Group 1: with congenital abnormalities, including Marfan syndrome and bicuspid aortic valve (n = 10) and Group 2: without congenital abnormalities (n =24). Consensus criteria (Halushka MK et al. Cardiovasc Pathol 2016; 25:247-57) and a scoring system (Waters KM et al. Cardiovasc Pathol 2017; 30:6-11) were used for pathology reporting. Independent T-test was done for statistical analysis.

Results: Patients in Group 1 were significantly younger than Group 2 (49.5 ±14.9 vs 61.9 ±16.8, $p < 0.03$). Vasa vasorum degeneration was insignificant between the 2 groups. No obvious atheromatous lesions in Group 1, but 5 cases in Group 2 had aortic atherosclerosis ($p <0.02$). Regarding medial degeneration no significant differences in elastic fiber fragmentation (4.4 ± 1.7 points vs 4.0± 1.5 points, $p = 0.5$), smooth muscle cell nuclei loss (2.2 ± 2.3 points vs 1.9 ± 2.2 points, $p= 0.7$), and laminar medial collapse (1.1 ± 1.4 vs 0.5 ± 1.2 points, $p = 0.2$) was seen between 2 groups. However, Group 1 had a significantly higher level of a mucoid extracellular matrix accumulation than Group 2 (4.7 ± 2.1 vs 2.6 ± 3.4 points, $p= 0.04$). Both groups had aortic wall weakness concentrated on the outer third of aortic media.

Conclusions: Aortic medial weakness is a common pathology in aortic dissection. Frequent surveillance and early prophylactic ascending aortic replacement is advised in congenital abnormalities group to reduce the risk of preventable type A dissection.

214 Papillary Muscle Rupture: A Single-Center Clinicopathological Study

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Background: Papillary muscle rupture (PMR) is a rare, life-threatening emergency causing acute mitral regurgitation resulting in cardiogenic shock. PMR produces surgical challenges resulting in severe complications and death. In this study, we provide

clinicopathological correlations that will help the pathologist effectively approach the surgical pathology of the ruptured papillary muscle.

Design: We retrospectively reviewed all surgical pathology cases with PMR diagnosis from 01/2006 to 04/2021. The patient demographics, clinical presentation and diagnosis, and clinical follow-up were assessed.

Results: Thirty-four cases were identified and were classified as 1) PMR due to coronary artery disease (CAD) or 2) PMR due to other etiologies. Group 1 represented 85% of cases (n=29) with a median age of 64 years. The time interval from symptom onset to diagnosis ranged from 1 to 14 days (median 4 days), and for most patients (n=24, 83%) this was their first myocardial infarction. Isolated involvement of the posteromedial papillary muscle (PM) was more common (n=21, 73%) than the anterolateral PM (n=5, 17%), or involvement of both PM (n=3, 10%). However, right coronary and left circumflex arteries were the culprit vessels in a similar number of cases (n=13 and n=11, respectively); the left anterior descending was the cause in only 3 cases (10%). In 3 cases, PMR occurred immediately or few hours after coronary artery intervention, suggesting reperfusion injury.

Group 2 was represented by 5 cases secondary to: 1) Infective endocarditis; 2) Trauma; 3) vascular type Ehlers-Danlos; 4) Iatrogenic (2 cases). The median age was 34 years. Histological findings in both groups showed ischemic-type changes. Coagulation necrosis, karyorrhexis of neutrophils and macrophages at the free border of the rupture were the most common findings (53%), compatible with less than a week-old MI.

Thirty patients underwent valve replacement and 4 patients underwent valve repair surgery. In-hospital mortality was 12% (2 cases from Group 1 and 2 cases from Group 2).

Table 1. Clinicopathologic characteristics of all patients with PMR

	PMR due to CAD (n=29)	**PMR due to other etiologies (n=5)**
Median age (years)	64 (40-83)	34 (27-75)
Patient age (years)		
<40	0	3 (60%)
40-70	18 (62%)	1 (20%)
>70	11 (38%)	1 (20%)
Sex		
Male	19 (65.5%)	4 (80%)
Female	10 (34.5%)	1 (20%)
History of prior MI		
Yes	5 (17%)	0
No	24 (83%)	5 (100%)
Culprit coronary artery		
Left anterior descending artery	3 (10%)	0
Left circumflex	11 (38%)	0
Right coronary artery	13 (45%)	0
Non-obstructive CAD	2 (7%)	1 (20%)
No evidence of CAD	0	4 (80%)
PM affected		
Anterolateral	5 (17%)	1 (20%)
Posteromedial	21 (73%)	1 (20%)
Anterolateral and posteromedial	3 (10%)	1 (20%)
Right ventricular PM	0	2 (40%)
Type of rupture		
Complete	29 (100%)	4 (80%)
Partial	0	1 (20%)
In-hospital mortality		
Yes	2 (7%)	2 (40%)
No	27 (93%)	3 (60%)

PM: papillary muscle; PMR: papillary muscle rupture, CAD: coronary artery disease

Conclusions: Microscopic findings in PMR are non-specific and reflect a common pathway of myocyte necrosis regardless of the etiology. Not all PMR is related to coronary artery disease, and pathologists need to consider pertinent clinical features to raise appropriate differential diagnoses to the clinical team. In patients <40 years old or in PMR affecting the right ventricle, uncommon etiologies need to be considered which may impact patient care and follow-up.

215 Glandular Heterotopia is More Common in Syndromic Than Non-Syndromic Cardiac Myxoma

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Background: Cardiac myxomas (CM) are benign neoplasms, with an uncertain histogenesis. They typically arise in an isolated fashion; however, some (fewer than 10%) occur in the context of the Carney complex (CNC). Heterotopic elements, including glands, may be seen histologically, and are postulated to arise from myxoma cells which are thought to have primitive multipotent lineage. Data on these glandular elements exists in case reports and small series, but little is known of their association, significance, or pathobiology.

Design: Institutional archives were queried for cases of cardiac myxoma (1985-2021). Salient clinical information was abstracted from the medical record, including age, sex, tumor location, history of adenocarcinoma, and presence or absence of a clinical diagnosis of CNC. Slides were retrospectively reviewed for glandular heterotopia. PRKAR1A immunohistochemistry was performed on all cases of cardiac myxoma with glandular elements and with available tissue.

Results: 188 cases were identified with slides available for review (22 with CNC). 9 cases (4.8%) had heterotopic glands documented on histologic evaluation, including 3 with CNC. The prevalence of glandular elements was higher in the CNC cohort (13.6%) compared to the non-CNC cohort (2.5%). No cases with glandular elements had a history of adenocarcinoma.

PRKAR1A staining was possible on 6 myxomas with glandular elements (including 1 with CNC). The CNC case showed loss of PRKAR1A reactivity in the myxoma cells. Three of the non-CNC cases also showed loss of staining in the myxoma cells, while the other two showed retention of PRKAR1A expression. PRKAR1A staining was concordant between myxoma cells and glands in all cases, although the glandular expression was weaker than that seen in the myxoma cells.

Conclusions: Glandular heterotopia occurs in <5% of cardiac myxomas and appears more common in the context of the Carney complex, where it can be seen in more than 10% of cases. This raises important questions as to the role of PRKAR1A and associated mechanisms in mesenchymal-epithelial transformation. Further, the concordant PRKAR1A expression profiles between the myxoma cells and glandular elements supports their common lineage.

216 Heart Allograft Acceptance is Associated with Quilty Lesions in Biopsies

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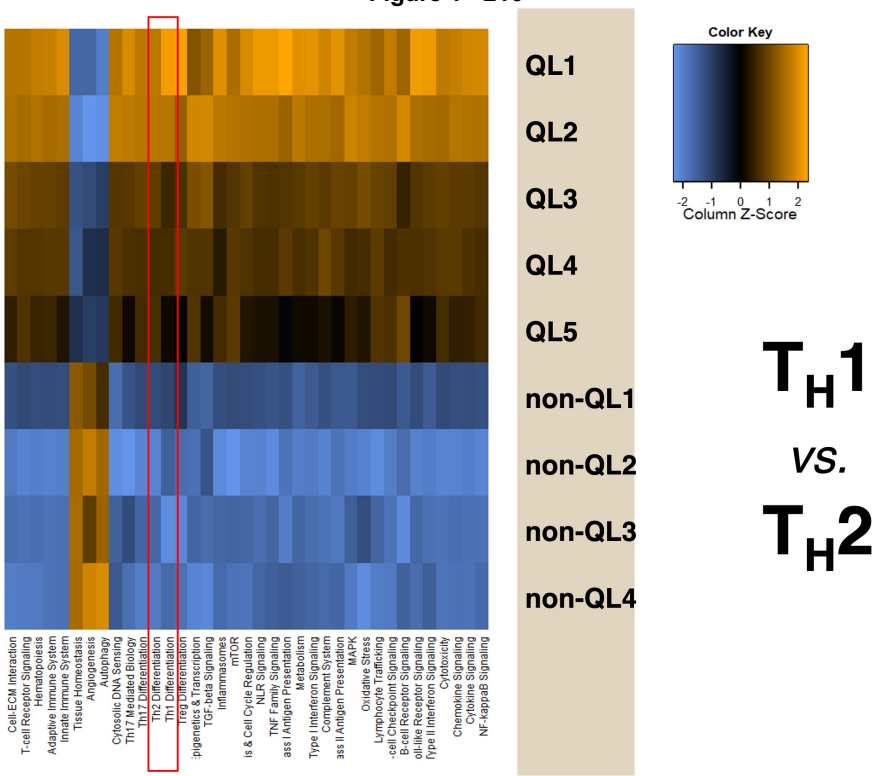
Background: Quilty lesions (QL) are defined as polytypic, commonly sub-endocardial lymphoid aggregates found in biopsies from heart transplants. Their appearance and presence in the cardiac tissue is still a mystery, with controversial findings of them being associated with rejection or acceptance of the allograft.

Design: 42 heart allograft biopsies from one institution were included in the study. Tissue was immunolabeled (IHC) for the T-cell markers CD4 and CD8, and the immune regulatory markers Fox-p3 and TGFbeta-1. A sub-set of 9 of these biopsies, 5 with QL and 4 without QL were selected for RNA extraction and gene analysis using the Nanostring n-Counter Human Orghan Transplant Immunology Panel (Seattle, WA).

Results: Biopsies with TGFbeta-1 (OR 1.4, p<0.05) and Foxp3 (OR 1.3, p<0.05) positive stain in QL were associated with better allograft acceptance. CD4 and CD8 stain in QL were not associated with rejection, however. interstitial CD4+<(p<0.04) and C<8+ (p<0.02) T-cells were associated with rejection.

The sub-set of biopsies with QL showed a predominance of adaptive type Th2 response over Th1 genes (3.88x vs. 3.15x). Particular regulatory genes (all p< 0.001) that were higher in biopsies with QL included TGFbeta1, IL10RA, Foxp3 and JAK3. Other pathways analyzed shows an upregulation of genes of cell-extracellular matrix interaction, adaptive immune response, innate immune response, Th17 mediated biology, T-reg differentiation, TGF-beta signaling, TNF family signaling and type I interferon signaling in biopsies with QL (Figure 1)

Figure 1 - 216



Conclusions: Heart allograft biopsies with QL showed a predominance of regulatory signals by both IHC and RNA gene analysis compared to biopsies without QL. QL, far from being passive bystanders, may have an immunomodulatory function in cardiac allografts.

217 Quilty Effect is Associated with Clinically Significant Acute T-cell Mediated Rejection, but Not with Antibody-Mediated Rejection

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Background: Quilty effect (QE) is defined as aggregates of subendocardial lymphocytes and can include foci of myocyte damage. QE occurs in up to 75% of cardiac transplant patients, and has no clear relationship with clinically actionable acute T-cell mediated rejection (ATCMR) or antibody-mediated rejection (AMR). We set out to explore the relationship between QE, ATCMR and AMR by correlating complete sets of endomyocardial biopsies (EMB) with markers of AMR and clinical outcomes.

Design: We reviewed all EMB from 50 patients transplanted from 2003-2018 for QE and histologic features of acute rejection, using the International Society of Heart and Lung Transplantation (ISHLT) system. QE was defined as a dense, subendocardial lymphocytic infiltrate, occupying >50% of a high power field. C4d immunofluorescent staining (Quidel, Athens, OH) was performed using the indirect method at 1:400 dilution. These findings were correlated with pre-and post-transplant donor specific antibodies (pre- and post-tx DSA) and clinical outcomes. Logistic regression analyses were used to determine odds ratio (OR).

Results: A median of 15 EMB (IQR 10, 21) from 15 children and 35 adults were reviewed (n = 847). QE was found on at least one biopsy in 68% of patients, at a median of 3.5 months and an average time to QE of 11.7 months. The median ratio of biopsies with QE to total EMB per patient was 0.28. For each additional biopsy there was an 11% increased chance of having QE (OR 1.11; p = 0.05). Of patients with QE, 44.1% (15/34) had grade 2R or 3R ATCMR on any biopsy (p=0.028). The odds of grade 2R or 3R rejection were over five-fold higher if QE was found on any biopsy (OR 5.53; p = 0.04). Pre-transplant DSA were 78% less likely if

QE was found on EMB (OR 0.22; p = 0.031). There was no significant association between QE and C4d positivity, post-tx DSA, AMR, transplant vasculopathy or death.

Fig. 1. EMB with microscopic features of ATCMR, ISHLT grade 3R (H&E X 100).

Fig. 2. EMB with QE on the left and focal myocyte damage on the right; this area would likely connect an area of QE were the tissue sectioned through (H&E x 200).

Figure 1 - 217

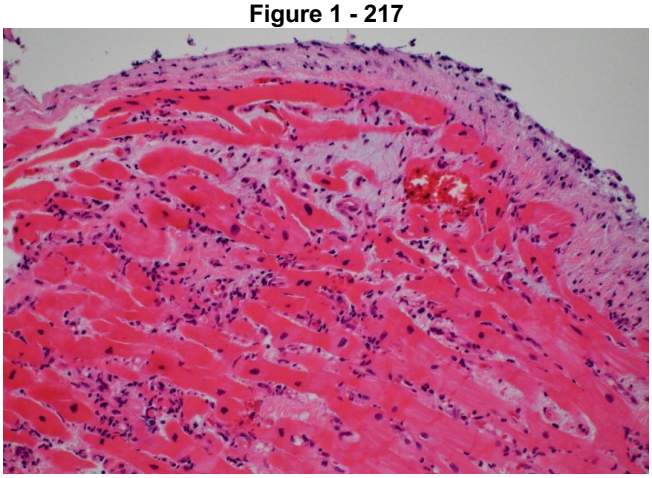
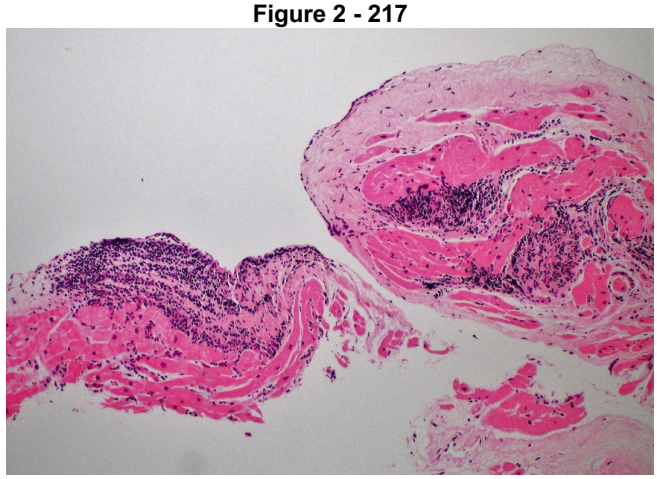


Figure 2 - 217



Conclusions: Almost 70% of patients had QE on at least one EMB. QE was associated with clinically significant ATCMR, with grade 2R or 3R rejection being five times higher over the transplant course if QE was seen on any biopsy. In contrast, QE was not associated with features of AMR, and was likewise not associated with poor clinical outcomes including transplant vasculopathy or death.