Med Path Rads Conference

5.10.13

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Objectives

- Define and understand noncompaction cardiomyopathy
- Briefly review normal intracardiac hemodynamic pressures and interpret a patient’s pressures
- List precipitating factors for decompensation of HF
- Briefly Review HF Evaluation
- Understand the types of complications after heart transplant
- Appreciate variability in the diagnosis of Antibody Mediated Rejection
Case Presentation

► CC fatigue, SOB
► HPI: Details deleted for website.
Details presented at conference regarding PMH, HPI, PE but deleted in this example.
Non-compaction Cardiomyopathy
or
Spongiform cardiomyopathy
Normal embryogenesis

During development, the majority of the heart muscle is a sponge-like meshwork of interwoven myocardial fibers. As normal development progresses, these trabeculated structures undergo significant compaction that transforms them from spongy to solid.

Noncompaction cardiomyopathy results when there is failure of this process of compaction.
Pathogenesis – disease of excessive trabeculation

- Extensive spongy transformation of LV myocardium with prominent coarse trabeculations

- Deep recesses of LV cavity, covered with endocardium ("pseudosinusoids") not communicating directly with epicardial coronary arteries.

- Loosely organized myocytes with focal compensatory hypertrophy, focal ischemic necrosis within endocardial layer, fibrous and elastin deposition.

- Often >5 trabeculations present.

- Trabeculated endocardial layer often at least 2x thicker than myocardium.

- Inferoapical, apical Lateral, mid-inferior and mid-lateral predisposition with rare involvement of IVS & basal distribution.

Left Ventricular Noncompaction

► Plausible Theories

1) Non-compaction Hypothesis – Embryonic compaction arrested due to primary genetic defect.

2) Compensation/Ischemic/Hemodynamic Hypothesis – Noncompaction as an adaptive reaction to abnormally contracted myocardium resulting from microcirculatory/metabolic dysfunction so as to increase surface area for gas exchange,

3) Myocarditis Hypothesis – Virally mediated (adenovirus and coxackievirus) subendocardial fibrosis
Historical Perspective

Characteristic intracardiac pressure wave forms during passage through the heart
CVP lumen is directly within the RA..... no delay.

PCWP opening is a substantial distance from LA, causing delay in pressure transmission.

So, PCWP waves and descents occur later on ECG.
4/19 RHC

- RA 16
- RV 29/16
- PA 28/18, mean 22
- PCW 18 Cardiac output 3.5 L/min, index 2.1 L/min/ M2
- Normal coronaries
- LV angio, moderate to severe diffuse hypokinesis, EF 35%, mild MR
- Endomyocardial biopsy completed.
2D ECHO 4/19
Dr. Benham Tehrani
4/19/13 Echo noted to have LVEF mildly reduced at 45%, mild MR, mild concentric LVH.

Echo on 2/14/13 shows a left ventricular end-diastolic dimension of 32mm with a left ventricular ejection fraction of 55%.
- PMNs 75%
- Lymphocytes 12%
- Monocytes 9%
- Eosinophils 3%

- Prot 7.1
- Alb 3.1
- Tbili 1.6
- AST 28
- ALT 32
- Alk Phos 70

Ca 9.3
Mg 1.8
Precipitating Factors for Decompensation of CHF

- Myocardial Ischemia or infarction
- Valvular dysfunction
- HTN
- Noncompliance with diet and medications
- Infection
- Comorbid condition (e.g., renal failure)
- Toxins
- Inappropriate Drug Therapy (negative inotrope, salt retention)
- High – output states (pregnancy, hyperthyroidism)
- Arrhythmia (often atrial fibrillation)
HF Evaluation

- CXR
- EKG
- CBC
- U/A
- CMP
- TSH
- Non-invasive stress testing – potential candidates for revascularization
- ECHO - evaluate structure of heart
- Coronary angiography – angina or signs of ACS
HF Evaluation

► Endomyocardial biopsy for patients with:

- Recent onset of rapidly deteriorating cardiac function, especially if characterized by chest pain, arrhythmias, and normal coronaries (eg. giant cell myocarditis)

- Systemic disease and possible cardiac involvement (eg. Hemochromatosis, sarcoid, amyloid)
ECHO 5/1
Dr. Benham Tehrani
5/1 ECHO

- LEFT VENTRICLE: Paradoxical septal motion suggested. Inferolateral akinesis suggested. Size was normal. Systolic function was moderately reduced. Ejection fraction was estimated to be 35 % in the range of 30 % to 40 %. There was moderate diffuse hypokinesis. Wall thickness was mildly to moderately increased.

- Changes have occurred since study of 4/19/13. LVEF is moderately depressed but difficult to quantify because of paradoxical septal motion.
Right heart catheterization:
- RA 26 v-35 mmHg
- RV 42/16 mmHg
- PA 40/24 mmHg and mean 31 mmHg
- PCWP 24 mmHg with v-waves 26 mmHg
- PA sat 51.0%
- Fick CO 2.74 L/min
- Fick CI 1.61 L/min/m2
- PVR 2.9 WU

Endomyocardial Biopsy:
- 4 endomyocardial biopsy specimens taken from the right ventricle and sent to pathology for review.
Pathology

Dr. Syed Zaman

Histological slides and path report shown during conference have been deleted in this example.
Histologic features of AMR (antibody mediated rejection)

- Myocardial capillary injury with endothelial swelling
- Interstitial edema/ hemorrhage
- Intravascular thrombi
- Myocyte necrosis with cellular infiltrate
ISHLT grading system

- Grade 0 = no rejection
- Grade 1A = focal perivascular infiltrate without necrosis
- Grade 1B = diffuse but sparse infiltrate without necrosis
- Grade 3A = multifocal aggressive infiltrate and/or myocyte necrosis
- Grade 3B = diffuse inflammation with necrosis
- Grade 4 = diffuse aggressive neutrophils +/- infiltrate, edema, hemorrhage, vasculitis, with necrosis
Old versus New grading (2004)

- 0 = 0
- 1A, 1B, 2 = 1R
- 3A = 2R
- 3B = 3R
Thought provoking questions

► Patient has morphological features of cellular rejection, and no morphologic features of antibody mediated rejection

► But is this Antibody mediated Rejection?

► What is the difference between antibody mediated rejection vs cellular rejection?

► Why is the Cd staining important?
Complications After Cardiac Transplant

► Early Complications
- Primary Graft Failure
- Hyperacute rejection
- Acute rejection
- Arrhythmia

► Late Complications
- Cardiac Allograft Vasculopathy
- CKD
- Infection
- Malignancy (Skin Cancer and post transplant lymphoproliferative disease)
Primary Graft Failure

- Common causes include ischemic injury and RHF due to pulmonary HTN
- Risk factors: extended cold ischemia time of the donor heart and elevated PVR in the recipient before transplant
- Accounts for 40% of deaths within the 1st 30 days after cardiac transplant
Hyperacute rejection

- Rare
- Donor heart is initially perfused with blood from recipient
- Caused by preformed donor-specific antibodies (high titers) from the recipient circulating within the coronary circulation of the donor heart
- Titer usually detected on pre-transplant screening
- Crossmatching with donors minimizes the risk
Acute Rejection

- T cell mediated (cellular immune response) OR recipient antibodies to donor antigens (humoral immune response)
- Does not really cause symptoms unless it is fulminant
- Detection is important because frequent episodes, especially in the 1st year, are associated with reduced graft survival and possibly with an increased incidence of cardiac allograft vasculopathy
- Biopsies are usually performed weekly for the 1st month, then every 2 weeks until 3 months after transplant, and frequency is less
- ISHLT grading system for acute cellular rejection has changed in 2004

13-point risk score is highly predictive of clinically significant rejection episodes within 1 year of orthotopic heart transplantation
Acute rejection (continued)

- **AMR**
  - less recognized and underdiagnosed
  - increased incidence of cardiac allograft vasculopathy and mortality
  - histologically – endothelial swelling, macrophages/PMNs in capillaries, fibrin deposition
  - immunofluorescence markers have changed over the years; and have failed to correlate with clinical severity
Acute rejection (continued)

► ISHLT - AMR diagnosis
- histologic findings
- immunopathologic findings (C3d and C4d staining)
- presence of donor specific antibodies
- allograft dysfunction

→ Methods to diagnosis though vary amongst institutions
→ 2/4 acceptable?

Balancing the Tightrope of Cardiac Allograft Rejection
Equations or Experience?
Mandeep R. Mehra, MD
Diagnostic dilemmas

- Arriving at the diagnosis can be variable b/c
- antibody mediated morphological features can overlap with cellular rejection
- there is no linear relationship between the phenotype of rejection and number of features
- in turn, studies to evaluate treatment strategies can be variable and it can be difficult to establish evidence based treatment guidelines
Brief Communication

A Survey of Current Practice for Antibody-Mediated Rejection in Heart Transplantation

S. Chih\textsuperscript{a}, K. J. Tinckam\textsuperscript{b} and H. J. Ross\textsuperscript{c,*}
evaluating current international practice for the management of AMR in heart transplantation according to ISHLT proposed pAMR grade
Arrhythmia

- Sinus tachycardia results from vagal denervation of the donor heart
- Sinus node function generally improves with time, but occasionally pacemaker implantation is required
- Late development of AV block is poor prognosis
- RBBB can occur and is often a result of prolonged cold ischemia time or injury to the Right bundle during biopsy
- Atrial fibrillation – (early) from healing or (later) rejection
- Other atrial tachycardias
Cardiac Allograft Vasculopathy (LATE)

- Leading cause of late morbidity and death among heart transplant recipients
- Angiographic studies indicate that CAV occurs in 42% of all heart transplant patients
- Diffuse process affects large epicardial vessels and the microcirculation
- Histology – concentric fibrous intimal hyperplasia, smooth muscle proliferation → luminal narrowing, reduction of myocardial blood flow
- Diagnosis – by coronary angiography
- Endothelial dysfunction and plaque formation may lead to rupture and ACS
Final diagnosis

- Antibody mediated rejection with acute graft failure
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