62 Year Old Man With Resistant Cardiac Constriction

Case Presentation

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62 Year Old Man Undergoing General Medical Examination

• Progressive dyspnea on exertion
• Peripheral edema

62 Year Old Man Undergoing General Medical Examination

Past Medical History

• Treated hypertension
• Previously diagnosed with rheumatoid arthritis
• Prior bilateral shoulder and hip arthroplasties

Medications

• Nebivolol 5 mg daily
  • Recently added
  • BP and HR better but he felt “awful” since starting it
• Furosemide 20 mg daily
• Simvastatin 40 mg each evening
• Prednisone 8 mg daily
• Celebrex 200 mg twice daily
• Previously had trials of methotrexate, Imuran and Adalimumab

62 Year Old Man Undergoing General Medical Examination

Physical Exam

• BP 115 / 80 mmHg  HR 80/min; irregular
  • No abnormal pulsus paradoxus
• JVP elevated with rapid descents
• Quiet precordium; 2+ right ventricular lift
• Intermittent apical diastolic sounds
• Lungs: bibasilar crackles
• Abd: probable ascites; no liver abnormalities
• Mild thigh pitting edema; 3+ leg and foot edema
62 Year Old Man With Dyspnea And Edema

**Normal Laboratory Tests**
- Hgb (13.5), RBC MCV and platelets (280 K)
- Na+, K+ and creatinine
- Glucose
- Total protein, AST, uric acid and TSH
- Troponin-T

**Abnormal Laboratory Tests**
- WBC (16,500 with left shift)
- Cardiac CRP 89 (nl <3)
- Decreased serum iron (normal TIBC)
- Alk phosph 145 (nl <115)
- INR 1.6
- Chol 83, TG 65, HDL 15 and LDL 55
- NT-ProBNP 2491

**Clinical Impression**
- Right greater than left-sided heart failure
- Indeterminate mechanism
- Clinical suspicion of HFpEF
  - Myocardial (restrictive) or
  - pericardial (constrictive) dysfunction

**Clinical Plan**
- Heparin anticoagulation
- IV diuretic
- Limited transthoracic echo
  - If reduced EF
    - Further evaluation
    - Initiation of appropriate drugs
  - If normal EF
    - TEE-guided cardioversion
    - Evaluation of diastole after SR restored
62 Year Old Man With Dyspnea And Edema

LV Intracavitary CW Doppler

Mitral PW Doppler
62 Year Old Man With Dyspnea And Edema
*Mitral Medial Annulus TDI*

62 Year Old Man With Dyspnea And Edema
*Mitral Annulus TDI*

62 Year Old Man With Dyspnea And Edema
*Tricuspid Annulus TDI*

62 Year Old Man With Dyspnea And Edema
*Hepatic Vein PW Doppler*

62 Year Old Man With Dyspnea And Edema
*Hepatic Veins*
62 Year Old Man With Dyspnea And Edema

Echo Impressions
- Findings consistent with constrictive pericarditis
  - Ventricular septal shift with respiration
  - Dilated inferior vena cava with no inspiratory collapse
  - Hepatic vein expiratory diastolic flow reversals
  - Preserved mitral medial annulus e' velocity
- Estimated LVEF 70%
- LV mid-intracavitary dynamic gradient
- Calcified mitral annulus and thickened mitral valve leaflets

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He underwent TEE-guided electrical cardioversion
- Successful restoration of sinus rhythm
- Not much change in symptoms after DCCV
- Based on hepatic ultrasound, GI consultant decided LFT abnormalities were all due to congestion
62 Year Old Man With Dyspnea And Edema

**Cardiac Catheterization**
- Findings typical and classic for constrictive pericarditis
  - Near-equalization of diastolic pressures in all chambers.
  - Atrial pressure waveform showed steep Y-descent and lack of inspiratory fall in mean atrial pressure (Kussmaul's sign)
  - Significant ventricular interdependence
  - Significant dissociation of intrathoracic and intracavitary pressures
- Normal coronary arteries

**GI Lab Tests**
- Alkaline phosphatase 157 (45-115)
- Normal AST and ALT
- GGT 80 (12-148)
- Total bilirubin 1.1 (0.1-1.0)
- Direct bilirubin 0.7 (0-0.3)
- Albumin 3.0 (3.5-5.0)
- Hepatic ultrasound
  - Liver appeared normal
  - Small amount of ascites

**Cardiac CT Scan**
- Moderate circumferential thickening of pericardium
- Inflammatory changes in adjacent fat
- Small pericardial effusion
- Persistent left to right bowing of ventricular septum
- Normal LV contractile function
- Moderate LA enlargement

**Rheumatology Consult**
- Clinically and radiographically consistent with rheumatoid arthritis
- However, RF and CCP antibodies were negative (unusual in RA with extra-articular manifestations)
- Continue current steroids; additional drug therapy not likely to quiet down his pericarditis
- Reconsider immunosuppressive therapy after cardiac surgery

**Cardiac Surgery**
- Severe active inflammation of pericardium
- Radical pericardectomy (using cardiopulmonary bypass)
- No post-op issues
- Discharged post-op day 5

**Pathology Report**
Findings consistent with clinical history of constrictive pericarditis and RA
- Parietal pericardium ranged in thickness from 0.1-0.6 cm
- No calcification
- Fibrous thickening
- Moderate nongranulomatous lymphoplasmacytic infiltrates; moderate neutrophilic infiltrates
- Microfocal calcification; no rheumatoid nodules
62 Year Old Man With Dyspnea And Edema
Follow-up 2 Months After Pericardiectomy

- He was placed on methotrexate 10 mg weekly, due to ↑CRP level and his extra-articular manifestations of RA
- Dyspnea and edema better, but not resolved
- No help from additional diuretic therapy

62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

- Persistent jugular venous distension with rapid Y-descent and positive Kussmaul’s sign
- Persistent RV lift
- Liver normal to palpation
- 3+ leg edema; no thigh edema
- NT-proBNP 866 (2491 preoperatively)
62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

Mitral Annulus TDI

Medial  Lateral

62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

IVC  Hepatic Vein

62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

No Mitral Leaflet SAM

62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

Tricuspid Regurgitation

62 Year Old Man With Dyspnea And Edema
Echo Report 2 months after pericardiectomy

- Hyperdynamic LV
- Hypokinetic RV; RVSP 45 mmHg
- Diastolic TR and dilated IVC consistent with elevated RV diastolic pressure
- Leftward ventricular septal shift
- No inspiratory decrease in mitral inflow velocity

62 Year Old Man With Dyspnea And Edema

- Differing opinions about the echo findings
  - RV systolic dysfunction versus
  - Residual constrictive physiology
- Clinical concern for residual visceral pericarditis
- Added digoxin for right ventricle
- Augmented diuretics
  - Higher dose loop diuretic
  - Added thiazide
62 Year Old Man With Dyspnea And Edema
Follow-up 3 Months After pericardiectomy

- Less edema and dyspnea
- Weight down 8 kg

Cardiovascular Physical Exam
- Borderline jugular venous distention
- Kussmaul's (+)
- Pericardial friction rub
- Trace leg edema
- NT-ProBNP 1412
- Metoprolol was discontinued because of fatigue

62 Year Old Man With Dyspnea And Edema
Echo 3 months after pericardiectomy

Constrictive physiology
- Normal LV size; EF 70%
- Increased pericarial thickness around RV free wall
- Enhanced ventricular interdependence
- Diastolic flow reversals in hepatic vein with expiration
- Mildly dilated IVC with reduced collapse
- RVSP 47 mmHg; systolic blood pressure 102 mmHg

62 Year Old Man With Dyspnea And Edema
Cardiac MRI 3 months after pericardiectomy

- The residual pericardium was thickened and enhanced with gadolinium
- Abnormal ventricular septal motion, but no definite enhanced ventricular interdependence
- Normal LV size; EF 60%
- Normal RV size; EF 56%
- Severe biatrial enlargement
- Mildly enlarged IVC

62 Year Old Man With Dyspnea And Edema
Follow-up 4 Months After pericardiectomy

- Exercises for 30 minutes at a time
- No dyspnea on exertion, orthopnea or PND
- Using furosemide intermittently for edema
- Jugular venous pressure still increased with positive Kussmaul's sign
- No pericardial rub
- NT-proBNP 1671

62 Year Old Man With Dyspnea And Edema
Rheumatology follow-up 4 months after pericardiectomy

- Joints symptoms under control
- Persistent marked increase in CRP (75.7)
- Active pericardial inflammation as an extra-articular manifestation of RA
- MTX dose increased to 15 mg weekly
62 Year Old Man With Dyspnea And Edema
Follow-up 6 Months After pericardiectomy
- Several weeks before he noted rapid palpitations and dyspnea and his peripheral edema increased
- Presented to local emergency department
  - Was in atrial flutter
  - Warfarin was started
  - Metoprolol was restarted
- Dyspnea resolved and no longer sensing palpitations

62 Year Old Man With Dyspnea And Edema
Follow-up 6 Months After pericardiectomy
- JVP normal but Kussmaul’s and HJR present
- Friction rub present
- Holosystolic murmur of TR
- Lungs clear
- No peripheral edema
- ESR 20; CRP 51.3
- NT-proBNP 948
- Metoprolol dose decreased (fatigue)

62 Year Old Man With Dyspnea And Edema
Follow-up 10 Months After pericardiectomy
- No dyspnea on exertion, orthopnea or PND
- Peripheral edema well controlled
- No jugular venous distention but still has Kussmaul’s sign and HJR
- 2/6 pericardial friction rub
- Lungs clear
- Mild liver enlargement and tenderness
- No peripheral edema

62 Year Old Man With Dyspnea And Edema
Follow-up 10 Months After pericardiectomy
- Persistent iron deficiency anemia
- ESR 39; CRP 99.5
- NT-proBNP 3595
- Warfarin discontinued and diuretics decreased
- Added IV rituximab; 2 infusions, 2 weeks apart (anti-B lymphocyte monoclonal antibody)
- Continued prednisone 8 mg daily and methotrexate 15 mg weekly

62 Year Old Man With Dyspnea And Edema
Hospitalized 11 months after pericardiectomy
- Progressive fatigue and loss of energy
- Progressive loss of muscle mass despite maintaining good nutrition
- Persistent cough but no dyspnea, orthopnea or PND
- Three episodes of syncope/near syncope, with falls

62 Year Old Man With Dyspnea And Edema
Hospitalized 11 months after pericardiectomy
- Jugular venous pressure 12 cm
- Persistent pericardial rub plus 2/6 systolic murmur at LSB
- Lungs: diffuse crackles bilaterally
- Mild lower leg edema
- Hb 10.8; ESR 20; CRP 99.6
- NT-ProBNP 4665
- 3.0 second pauses noted on monitor; digoxin was held
62 Year Old Man With Dyspnea And Edema

**Dynamic Intraventricular Gradient**

CW Doppler through LV cavity

3.1 m/sec

62 Year Old Man With Dyspnea And Edema

**Hospitalization 11 months after pericardectomy**

- Developed SVT off digoxin
- Oral diltiazem 30 mg initiated
- After second dose, he had a 5-sec pause with symptom prodrome similar to out-patient episodes
- This was followed by a 12-sec pause with LOC
- Transferred to CCU, and TTVPMP placed
- Subsequently underwent placement of dual chamber permanent pacing system

62 Year Old Man With Dyspnea And Edema

**Echo 11 months after pericardectomy**

- No convincing signs of residual constriction
- Normal LV size; estimated EF 65-70%
- Dynamic LV intracavitary obstruction
- Mitral stenosis; MG 12 mmHg (HR 88/min)
- Mild to moderate tricuspid regurgitation
- RVSP 39 mmHg
- Borderline IVC dilatation with reduced inspiratory collapse

62 Year Old Man With Dyspnea And Edema

**Hospitalization 11 months after pericardectomy**

- PET scan demonstrated lymphadenopathy in mediastinum, retroperitoneum and bilateral iliac chains
- EGD with biopsy
- HIV studies negative
- Consultations with GI, Hematology and Rheumatology
- IV iron administered for persistent iron deficiency and inability to tolerate oral iron

62 Year Old Man With Dyspnea And Edema
62 Year Old Man With Dyspnea And Edema
Complex Hospitalization

- PCR for Whipple disease negative x 2
- Serology for celiac sprue negative
- EGD (again): 2cm DH; otherwise normal
  - Normal small bowel mucosa on biopsy
  - No evidence of Whipple’s disease, celiac sprue or giardia
- Colonoscopy was normal

- His cough was attributed to pneumonia and treated with levofloxacin and flagyl
- IV furosemide administered and then he was transitioned to oral diuretic
- Metoprolol tartrate added to decrease LV intracavitary gradient
- Prednisone, methotrexate and rituximab were continued

12 months after pericardectomy

- Rheumatologist requested further testing on specimens removed at pericardiectomy
- PAS stain of pericardium showed microorganisms
- These were confirmed as Tropheryma whipelii by PCR on the pericardial tissue

Infectious Diseases Consultation

- Whipple’s Disease would fit with
  - Years of seronegative arthritis
  - Pericarditis
  - Profound weight loss and fatigue
  - Anemia
  - Elevated inflammatory markers
- Unusual to have no diarrhea associated with the major weight loss*
  *Usual weight loss mechanism is malabsorption, which results in diarrhea/steatorrhea

He was started on ceftriaxone 2 grams IV daily for two weeks
- Trimethoprim/sulfamethoxasole DS twice daily for one year
- Methotrexate was discontinued
- He subsequently underwent steroid taper
62 Year Old Man With Dyspnea And Edema
Follow-up 2 months after antibiotic therapy initiated

- Putting on muscle mass
- No exertional dyspnea
- Variable amount of lower extremity edema, for which he self-adjusts furosemide
- No further syncope
- Hb 13.0; ESR 17; CRP 15.1
- NT-ProBNP 596

62 Year Old Man With Dyspnea And Edema
Follow-up 8 months after antibiotic therapy initiated

- Markedly improved quality of life
- Gained 40 pounds
- Aerobic exercise three times weekly with no dyspnea (on metoprolol and furosemide)
- Normal to near-normal JVP
- No pericardial rub
- No symptoms of inflammatory arthritis
- Hb 14.1; ESR 10; CRP 7.8; NT-ProBNP 459

62 Year Old Man With Dyspnea And Edema
Echo 8 months after antibiotic therapy initiated

- No constrictive physiology
- Small LV cavity; EF 72%
- RV enlargement with decreased function
- RVSP 23 mmHg
- Thickened AV with mild to moderate AR
- Thickened and calcified MV
  - MG 5 mm Hg (HR 60/min)
  - Valve area (t ½) 2.4 cm²

62 Year Old Man With Dyspnea And Edema
Follow-up Four Years after Antibiotic Rx

- Exercising three times weekly (bike)
- No dyspnea or orthopnea
- JVP normal; no pericardial rub
- Hb 15.2
- NT-ProBNP 476

Whipple’s Disease

- Systemic bacterial infection
  - Fatal if untreated
- Causative organism: Tropheryma whippelii
  - Slow-growing, gram-positive bacillus
  - Present in the general environment

Lancet 361; 2003; 837-44
Whipple’s Disease

- First described by George H. Whipple in 1907
- Patient was 35 year old medical missionary
- Whipple referred to the disease as “intestinal lipodystrophy”
- Long thought to be an infectious disease
- Causative organism fully identified in 1992 by PCR applied to stored tissue from original patient

Whipple’s Disease
Epidemiology

- About 1000 cases reported
  - Asymptomatic carriers common
- Host
  - Majority are white males
  - Mean age 49 yrs
- Exposure risk
  - Farming and other outdoor occupations
  - Soil and animal contact (66% of cases)
  - Probable oral transmission

Whipple’s Disease
Clinical Manifestations

- Fever
- Weight loss
- Diarrhea/steatorrhea
- Abdominal pain
- Severe wasting syndrome
  - Enlarged abdominal lymph nodes
  - Hypoalbuminemia
- Arthralgias / arthritis
  - Large joints
  - Migratory
  - Can be destructive
- CNS involvement (late manifestation)

Whipple’s Disease
Cardiac Involvement

- Frequent (17-55%) (Pericardium, myocardium, endocardium)
- Autopsy series of 19 cases
  - 79% had adhesive pericarditis
  - 53% had fibrosis and deformity of cardiac valve(s), mainly mitral
  - 11% had myocardial fibrosis
- Constrictive pericarditis: 6 reported cases

- Arrhythmias
  - Sudden cardiac death
- Culture negative endocarditis
  - 17 cases described
  - GI disease or arthritis not always present
  - Prominent fibrosis with only slight inflammation
  - Diagnosed by PCR on valvular tissue

Whipple’s Disease
Diagnosis

- Elevated acute phase reactants
- No serologic tests
- EGD with small bowel biopsies
  - PAS staining shows magenta-stained inclusions within macrophages
**Whipple’s Disease**

**Diagnosis**
Polymerase chain reaction (PCR) on
- Lymph nodes
- Heart valve
- Synovial fluid
- CSF
- Blood (low sensitivity)


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**Whipple’s Disease**

**Treatment**
- Fatal in pre-antibiotic era
- Antibiotic regimen
  - Ceftriaxone
    - 2 g IV daily for 2 weeks
  - Trimethoprim/Sulfamethoxazole DS
    - Twice daily for one year
- Immune reconstitution inflammatory syndrome in 10%
- Relapses possible

*Gastroenterology 138; 2010; 478-86
Ann Intern Med 153; 2010; 710-7*

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**Relevant to this patient . . .**
- Long prodromal stage
  - Duration of articular symptoms before diagnosis
    - Mean 6.7 years (range 0.3 – 28)
- Classic signs and symptoms absent in ~15%
  - He had no diarrhea
- Immunosuppression
  - Rapid clinical progression
  - He was treated with Corticosteroids and anti-TNF therapy

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**Questions & Discussion**
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