



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 With Dyspnea And Edema *Past Medical History*

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

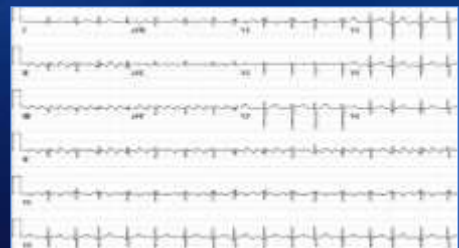
62 Year Old Man With Dyspnea And Edema *Medications*

- 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

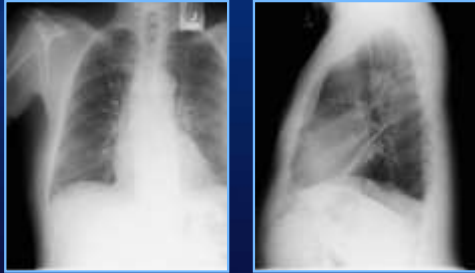
62 Year Old Man With Dyspnea And Edema *Physical Exam*

- 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



62 Year Old Man With Dyspnea And 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

62 Year Old Man With Dyspnea And Edema *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

62 Year Old Man With Dyspnea And Edema *Clinical Impression*

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

62 Year Old Man With Dyspnea And Edema *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



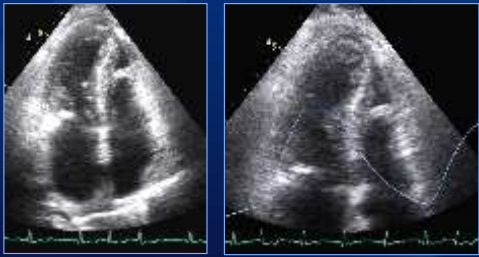
62 Year Old Man With Dyspnea And Edema



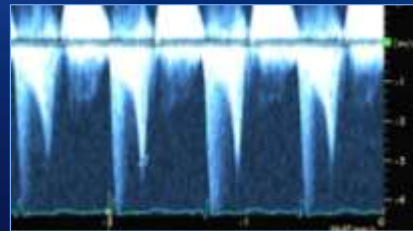
62 Year Old Man With Dyspnea And Edema



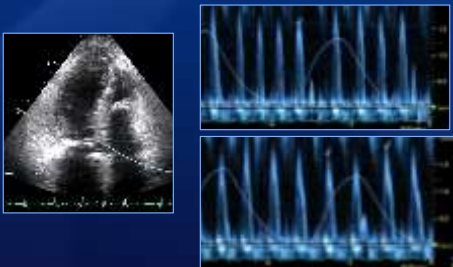
62 Year Old Man With Dyspnea And Edema



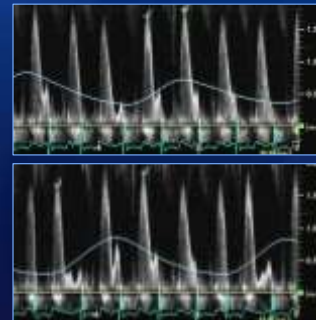
62 Year Old Man With Dyspnea And Edema
LV Intracavitary CW Doppler



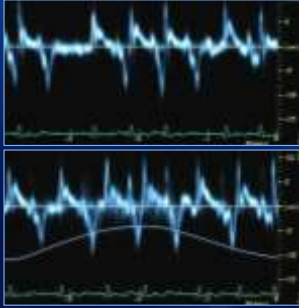
62 Year Old Man With Dyspnea And Edema



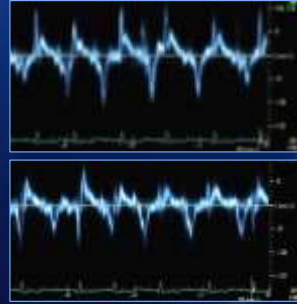
62 Year Old Man With Dyspnea And Edema
Mitral PW Doppler



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



62 Year Old Man With Dyspnea And Edema
Mitral Annulus TDI

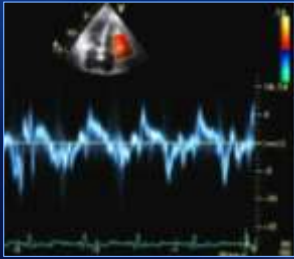


Medial

Lateral



62 Year Old Man With Dyspnea And Edema
Tricuspid Annulus TDI

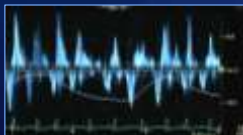


62 Year Old Man With Dyspnea And Edema



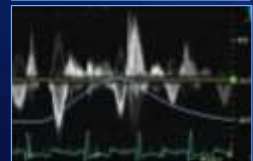
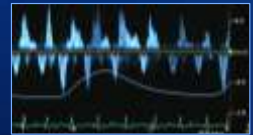
62 Year Old Man With Dyspnea And Edema

Hepatic Vein PW Doppler

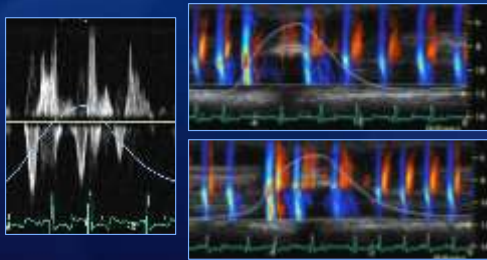


62 Year Old Man With Dyspnea And Edema

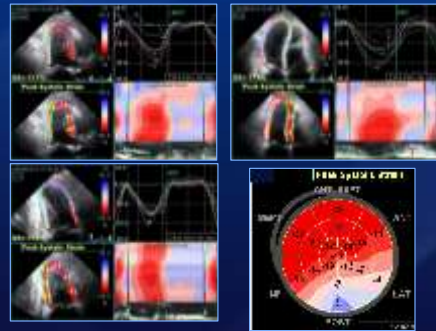
Hepatic Veins



62 Year Old Man With Dyspnea And Edema
Hepatic Vein



62 Year Old Man With Dyspnea And Edema



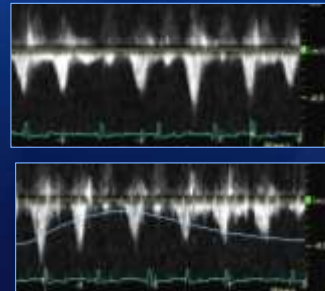
62 Year Old Man With Dyspnea And Edema
LV Longitudinal Strain



GLPSS
-16%



62 Year Old Man With Dyspnea And Edema
SVC PW Doppler



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



62 Year Old Man With Dyspnea And Edema

- Dyspnea and peripheral edema improved with diuresis
- 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



62 Year Old Man With Dyspnea And Edema *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



62 Year Old Man With Dyspnea And Edema *Cardiac CT Scan*

Constrictive Pericarditis

- 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



62 Year Old Man With Dyspnea And Edema *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



62 Year Old Man With Dyspnea And Edema *Cardiac Surgery*

- Severe active inflammation of pericardium
- Radical pericardiectomy (using cardiopulmonary bypass)
- No post-op issues
- Discharged post-op day 5



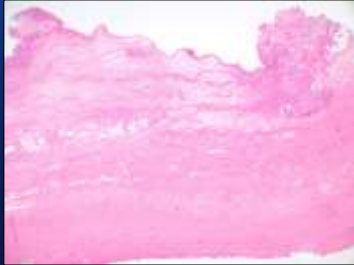
62 Year Old Man With Dyspnea And Edema *Pathology Report*

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



Parietal Pericardium



H&E



Parietal Pericardium



H&E



62 Year Old Man With Dyspnea And Edema Follow-up 2 Months After Pericardiectomy

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

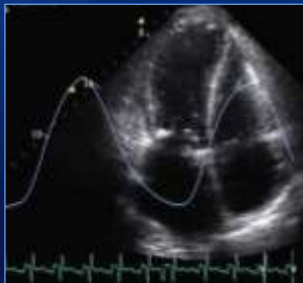


62 Year Old Man With Dyspnea And Edema Two Month Follow-up

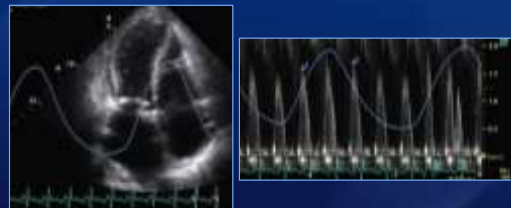
- Persistent jugular venous distension with rapid Y-descent and positive Kussmaul's sign
- Persistent RV lift
- Liver normal to palpation
- 3+ leg edema; no thigh edema
- NT-proBNP 866 (2491 preoperatively)



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

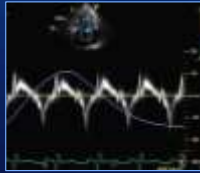


62 Year Old Man With Dyspnea And Edema Two Month Follow-up

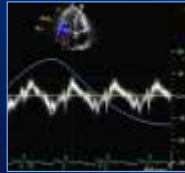


62 Year Old Man With Dyspnea And Edema
Two Month Follow-up

Mitral Annulus TDI

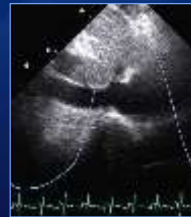


Medial

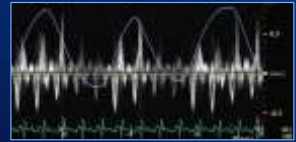


Lateral

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

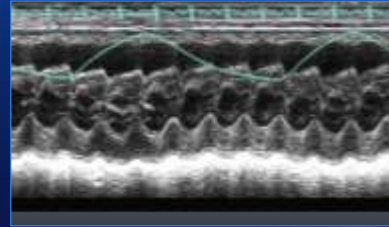
Follow-up 3 Months After pericardiectomy

- 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



62 Year Old Man With Dyspnea And Edema

Echo 3 months after pericardiectomy

Constrictive physiology

- Normal LV size; EF 70%
- Increased pericardial 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

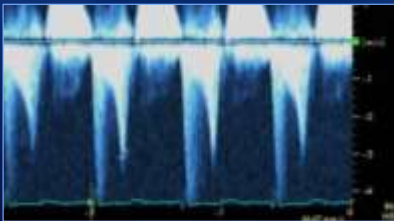


62 Year Old Man With Dyspnea And Edema



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 *Echo 11 months after pericardiectomy*

- 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 pericardiectomy*

- 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 TTVPM placed
- Subsequently underwent placement of dual chamber permanent pacing system



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

- 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 *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



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

- 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

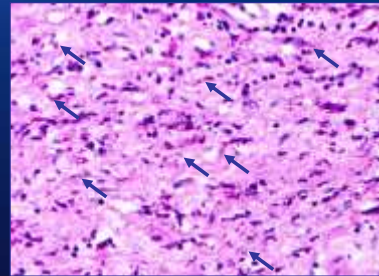


62 Year Old Man With Dyspnea And Edema *12 months after pericardiectomy*

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



Parietal Pericardium *Inclusions Within Macrophages*



PAS-D



62 Year Old Man With Dyspnea And Edema *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



62 Year Old Man With Dyspnea And Edema *Infectious Diseases Consultation*

- He was started on ceftriaxone 2 grams IV daily for two weeks
- Trimethoprim/sulfamethoxazole 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 1/2) 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 whipplei*
 - Slow-growing, gram-positive bacillus
 - Present in the general environment



N Engl J Med 342; 2000; :620-5
 Lancet 361; 2003; :637-44



Immunohistochemistry of Tropheryma whipplei in Intestinal Tissues from Dr. Whipple's 1907 Patient

... [Detailed text describing the immunohistochemical findings in the 1907 patient's tissues, including the identification of Tropheryma whipplei in the intestinal mucosa and its association with the disease.]

Immunohistochemistry of Tropheryma whipplei in Intestinal Tissues from Dr. Whipple's 1907 Patient

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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



N England J Med 356; 2007; :55-66

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)



N England J Med 356; 2007; :55-66

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**



Circulation 52; 1975; 152-6
Can J Cardiol 25; 2009; e89-91

Whipple's Disease

Cardiac Involvement

- 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



N England J Med 356; 2007; 55-66
Can J Cardiol 12; 1996; 831-4

Whipple's Disease

Diagnosis

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



N England J Med 356; 2007; 55-66

Whipple's Disease Diagnosis

Polymerase chain reaction (PCR) on

- Lymph nodes
- Heart valve
- Synovial fluid
- CSF
- Blood (low sensitivity)

N England J Med 356; 2007; 55-66



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



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



Questions & Discussion

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