GIANT CELL MYOCARDIATIS

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HEART FAILURE AND HEART TRANSPLANTATION FELLOWSHIP
RHC
• A previously healthy 54-year-old female
• Presented with acute onset of malaise, nausea, palpitations, and presyncope.
• ECG showed monomorphic ventricular tachycardia at 230 bpm
• successful cardioversion. Hemodynamic stability was restored
• Initial cardiovascular examination
  • positive abdominojugular reflux sign and a third heart sound.
  • No clinical evidence of pulmonary or systemic congestion or low cardiac output state
• No other manifestations of systemic disorders were present.
• ECG in sinus rhythm revealed
  • Nonspecific intraventricular conduction delay with a QRS duration of 130 ms
  • QTc of 507 ms at a heart rate of 96 bpm.
• Transthoracic echocardiography
  • left ventricular systolic dysfunction with an estimated ejection fraction of 35%
  • preserved right ventricular function, and no valvular abnormalities
• SCA: Normal Coronary arteries
• Lab data:
  • CBC: Hgb=14 g/l with an MCV of 92 fl, platelet count of 182000, a WBC 12300 with a normal differential
  • a high-sensitivity troponin T of 46 ng/l
  • an NT-proBNP of 261 ng/l
  • an ESR of 11 mm/h, and a CRP of 3.2 mg/l
  • An infectious panel was negative for cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C, herpes simplex virus, HIV, mumps, toxoplasmosis, and varicella.
• On cardiac magnetic resonance imaging, there was extensive, midwall patchy late gadolinium enhancement consistent with acute myocarditis
RIGHT VENTRICULAR ENDOMYOCARDIAL BIOPSY
Inflamed/damaged area

Normal endomyocardium

Many multinucleated giant cells (H&E 20x)

Multinucleated giant cells (H&E 40x)

Mixed inflammatory cells including lymphocytes, eosinophils, histiocytes, and rare plasma cells

Eosinophils with degranulation
• Standard heart failure therapy
  • beta-blocker
  • angiotensin receptor inhibitor
  • mineral corticoid receptor antagonist.

• combined immunosuppressive therapy
  • High-dose prednisone (60 mg daily)
  • Tacrolimus
  • Mycophenolate mofetil

• dual chamber ICD

• Total hospital stay was 16 days

• Her echocardiogram at 6 and 12 months is unchanged
GIANT-CELL MYOCARDITIS

• A rare, rapidly progressive, and frequently fatal myocardial disease
• No sex predominance
• T lymphocyte-mediated inflammation of the heart muscle
• The reported incidence of GCM 0.007% and 0.051%
• Is associated with systemic autoimmune diseases in ≈20% of cases
  • Inflammatory bowel disease, thyroiditis, and thymoma
  • Cancer patients treated with immune checkpoint inhibitors
• The most common early manifestations
  • Heart failure
    • The most common presentation
    • Rapidly progressive
  • Ventricular arrhythmias
  • Atrioventricular block
  • Acute myocardial infarction
  • Unexpected sudden cardiac death
ELECTROCARDIOGRAM

- sinus tachycardia
- PR/QRS/QT prolongation
- Q waves
- local or diffuse ST-segment elevation
- diffuse T-wave inversion
- high-grade AV block
- ventricular arrhythmias
- normal ECG does not rule out GCM.
CARDIAC BIOMARKERS

• Biomarkers suggestive of myocardial injury
  • Troponin
• Brain natriuretic peptide
Echocardiographic findings
- nonspecific and variable
- normal
- LV systolic dysfunction
- increased LV wall thickness (due to myocardial edema)
- LV dilatation
- or aneurysm formation with mural thrombus.
- decline in longitudinal or circumferential strain may be diagnostic and prognostic

Cardiac magnetic resonance
- Edema
- Hyperemia
- LGE
- sensitivity of 78% to 80% and specificity of 87% to 88%
- location, pattern, and extent of LGE
- guide EMB

FDG-PET
- active inflammation
- guide EMB
- identifying lymph nodes as a target site for biopsy to rule out cardiac sarcoidosis (CS)
ENDOMYOCARDIAL BIOPSY

- should be strongly considered
- A total of 5 to 6 samples
- from more than 1 region of the RV septum
- The pathognomonic histological features
  - diffuse or multifocal inflammatory infiltrates that consist of lymphocytes with multinucleated giant cells and associated myocyte damage
  - giant cells are typically associated with intact or degranulated eosinophils
  - Fibrosis is usually mild if present
  - well-organized follicular granulomas containing central giant-cells exclude the diagnosis
- has reasonably high sensitivity
  - is significantly lower in patients with milder forms of GCM
- imaging-guided EMB
- Guided EMB by Electroanatomic mapping
OVERLAP WITH OTHER INFLAMMATORY CARDIOMYOPATHIES

- lymphocytic or eosinophilic myocarditis
- immune checkpoint inhibitor–associated myocarditis
- CS
  - more prevalent in Blacks
  - The duration from symptom onset to presentation and diagnosis is greater
  - Syncope, high-degree AV block, and permanent pacemaker implantation are more frequent
  - noncaseating granulomas and fibrosis
  - mere presence of giant cells does not distinguish these 2 entities
IMMUNOSUPPRESSIVE THERAPY

• involves 2 or 3 drugs
• corticosteroids and at least 1, and most often 2 additional immunosuppressive agents
• The rate of death or cardiac transplantation at 1 year without immunosuppressive therapy was 100%, with a median TFS of <3 months after symptom onset
• TFS rates improved significantly to 69% at 1 year, 58% at 2 years, and 52% at 5 years with combination immunosuppression
• 1 year after initial treatment, azathioprine or mycophenolate is discontinued and prednisone may be tapered off slowly in patients with normalization of LV function
• Cyclosporine or Tacrolimus is often continued indefinitely
• Alemtuzumab and sirolimus have been successfully used to treat 2 patients with recurrent post-cardiac transplant GCM
Alemtuzumab 15 mg x 2 days or 30 mg once (for refractory GCM)

Cyclosporine (12th hour trough: 150-375 ng/ml)

Azathioprine 1.5-2 mg/kg/day
OR
Mycophenolate mofetil

Cyclosporine (12th hour trough: 150-375 ng/ml)
OR
Tacrolimus (12th hour trough: 10-15 ng/ml in first 6 months, 5-10 ng/ml thereafter)

Methylprednisolone IV 1 g/day

Prednisone 1 mg/kg
OR
Slow taper

5 mg daily

Prednisone tapered off if LVEF normalizes

3 days
10 days
1 year
NEUROHORMONAL THERAPY

- maximally tolerated GDMT
- beta-blockers
- angiotensin converting enzyme inhibitors
- or angiotensin receptor blockers
- or angiotensin receptor blocker-neprilysin inhibitors
- and aldosterone antagonists
ANTIARRHYTHMICS AND IMPLANTABLE CARDIOVERTERDEFIBRILLATOR

- Management of arrhythmias in patients with GCM is similar to that in other types of cardiomyopathies.
- Advanced conduction system disease may require temporary pacing, frequently followed by permanent pacemaker implantation.
- Ventricular fibrillation or hemodynamically unstable VT
  - antiarrhythmic medications such as amiodarone
  - ICD for secondary prevention, if meaningful survival >1 year is expected
- Primary prevention?
  - LVEF <35%, despite at least 3 months of GDMT
  - extensive LGE on CMR despite adequate immunosuppressive therapy
  - particularly those with ventricular arrhythmias or ectopy on presentation or on ambulatory rhythm monitoring
  - high-grade fibrosis on EMB.
EXERCISE LIMITATION

• Should be restricted from participation in competitive sports or similar activities for at least 3 to 6 months

• Follow-up testing with cardiac biomarkers (cTn), an echocardiogram, ambulatory rhythm monitoring, and exercise tolerance testing

• Significant LGE on CMR
  • repeat CMR assessment before resuming exercise?
    • may be reasonable
INOTROPES, MECHANICAL CIRCULATORY SUPPORT, AND CARDIAC TRANSPLANTATION

- hemodynamic instability
  - inotropic therapy and/or temporary MCS
  - VAD) implantation has been associated with a higher risk of GCM recurrence in the allograft
- transplantation is a reasonable option
  - present more acutely
  - have increased rates of acute rejection
  - Post-transplant survival is similar to other etiologies
  - Recurrent GCM after transplantation occurs in 20% to 25% of patients
    - HF or other symptoms
    - Asymptomatic: detected on surveillance EMB
    - steroid pulse, followed by a taper:
      - asymptomatic recurrent GCM with normal LV function
    - Higher dose corticosteroids and ATG
      - recurrent GCM and LV dysfunction
    - Sirolimus and Rixuximab and Alemtuzumab