A Woman With Chest Pain, Syncope, and Transaminitis

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Case Presentation

The patient is a 49 year-old female with past medical history of anxiety and hyperlipidemia who presented to an outside hospital with complaints of five hours of substernal chest pain followed by three episodes of syncope witnessed by her son. At presentation in the emergency department the patient denied any current chest pain or shortness of breath. She received 325 mg of aspirin en route to the hospital by EMS. Her vital signs were temperature 100° Fahrenheit, heart rate 60 beats/minute, blood pressure 101/50 mm Hg, respiratory rate 20 breaths/minute, and a pulse oxygenation of 98% on room air. The patient's EKG showed ST elevations in the inferior leads. The patient's laboratory studies were: white blood cell (wbc) count 14 B/L, hemoglobin 13.2 g/dL, platelets 153 B/L, CKMB 32 U/L, troponin 8.27 ug/L, and CK 24.5 U/L. The patient was started on intravenous heparin and integrillin drips and transferred to Jefferson for emergent cardiac catheterization.

The patient had left and right coronary angiography which showed no evidence of occlusive coronary disease. Left heart catheterization demonstrated moderate to severe inferoapical hypokinesis and a mildly depressed left ventricular ejection fraction (40%). During the procedure, the patient was noted to have 2:1 AV heart block with intraventricular conduction delay, and a temporary transvenous pacemaker was placed. The patient was then transferred to the cardiac care unit.

In the cardiac care unit, the patient reported that she had no known drug allergies. Her only outpatient medication was a statin that was started six weeks ago. The patient denied any past surgical history. The patient consumed alcohol socially, had a 15 pack year history of smoking, and no history of illicit drug use. The patient's father died of a myocardial infarction at age 62, and the patient's mother was alive with a history of diabetes mellitus and arrhthymia. The patient noted that she had some nasal congestion for two days prior to the chest pain and syncope. The patient also reported working in her garden with rose bushes and was certain that she had a neck rash due to poison oak. Lastly, the patient reported decreased oral intake for the past two days due to "flu-like" disease.

Overnight, the patient had multiple episodes of bradycardia that warranted venous pacing on telemetry. Significant laboratory studies were: wbc 4.3 B/L, AST 539 U/L, ALT 313 U/L, and troponin 14.7 ug/L. The patient underwent successful implantation of a dual chamber VDD pacemaker. A transthoracic echocardiogram demonstrated an ejection fraction of 60%, mild to moderate mitral regurgitation, and an inferior vena cava normal in size without inspiratory collapse. The patient was transferred to the telemetry floor service.

On the third hospital day, the patient had no overnight complaints and wanted to be discharged home. Significant laboratory studies were a troponin of 16.5 and AST 299 U/L, and ALT 250 U/L. The patient had a CT of her head which showed no fracture or bleed. A CT of her chest demonstrated multifocal pneumonia with bilateral pleural effusions and subcentimeter pulmonary nodules. The patient was diagnosed with pneumonia and was started on ceftriaxone, azithromycin and flagyl.

On the fourth hospital day, the patient had an overnight fever of 100.7° Fahrenheit and an episode of oxygen desaturation to 89% on 2 liters oxygen via nasal cannula. Significant laboratory studies were: wbc 14.9 B/L, troponin 14.1 ug/L, AST 247 U/L, and ALT 240 U/L.

On the morning of the fifth hospital day, the patient had a fever of 100.6° Fahrenheit and an episode of tachycardia with oxygen desaturation to 75% on 2 liters with an increased respiratory rate (18 to 28 breaths/minute). An arterial blood gas showed pH 7.50, pCO2 23, PO2 138, HCO3 18, O2 sat 99%. Significant laboratory studies were wbc 18.9 B/L, troponin 8.9 ug/L, AST 279 U/L, ALT 288 U/L, lactate 40.8 mmol/L, and BNP 2058. The patient was treated with nebulizer treatments, intravenous furosemide, and an anxiolytic. A transthoracic echocardiogram demonstrated an ejection fraction of 25%, moderate-severe mitral regurgitation, severely decreased left ventricular systolic function with segmental wall motion abnormalities, mild right atrial enlargement, dilated inferior vena cava, and right ventricular enlargement with decreased function.

Later in the afternoon, the patient had complaints of shortness of breath and increased anxiety. Vital signs at the time were heart rate 123 bpm, blood pressure 100/60 mm Hg, respiratory rate 36 breaths/minute, pulse oxygenation of 90% on 100% non-rebreather mask. An arterial blood gas demonstrated pH 7.49, pCO2 27, PO2 60, HCO3 20, O2 sat 93%. The patient was once again treated with nebulizer treatments, intravenous lasix and had symptomatic relief. Three hours later, the patient had worsening respiratory distress and was found to have a respiratory rate of 48-60 with a pulse oxygenation of 68% on room air and 88% on 100% non-rebreather mask. A rapid response was called for worsening respiratory distress.

The patient was transferred to the cardiac care unit and emergently intubated. Subsequently, the patient became progressively hypotensive and a central line was placed, and intravenous norepinephrine was started. The patient was presumed to have worsening sepsis secondary to multifocal pneumonia with cardiomyopathy of sepsis. Antibiotic coverage was broadened to vancomycin and zosyn. In addition, doxycycline was added to cover possible ricketsial infections. A complete rheumatologic and autoimmune work up was sent for laboratory studies.

The following day, the patient had a transesophageal echocardiogram which showed no vegetations. Azithromycin was added to cover atypical organisms, and the patient was started

on an acute respiratory distress syndrome ventilator protocol. Significant laboratory studies were: wbc 23.1B/L with 6% bands, AST 1209 U/L, ALT 873 U/L, and troponin 6.29 ug/L.

On the seventh day, the patient underwent fiberoptic bronchoscopy which was grossly normal and bronchoalveolar lavage of the right upper lobe was sent for cultures. Significant laboratory studies were: wbc 19.1 U/L, creatinine 1.5 umol/L, AST 2220 U/L, and ALT 1516 U/L. The patient became progressively more hypotensive, and the norepinephrine drip was titrated. The patient also had decreasing urine output and worsening transaminitis was thought to be due to ischemic hepatitis.

On the eighth day, the patient developed a supraventricular tachycardia which was treated with adenosine and revealed an underlying atrial flutter rhythm. The patient was started on digoxin for rate control. With worsening hypotension and tachycardia, the patient was started on phenylephrine with plans to wean down norepinephrine. Due to worsening clinical status, Xigris therapy was also initiated. A transthoracic echocardiogram showed an ejection fraction of 10%, moderate-severe mitral regurgitation, severe left ventricular systolic function (with only the basal-inferolateral segment contracting – the remainder was hypokinetic/akinetic), right ventricular enlargement, moderate-severe tricuspid regurgitation. Late in the evening, the patient's clinical exam had a significant change with cool extremities and hypothermia. Laboratory studies were consistent with a state of disseminated intravascular coagulation and worsening renal function. A family meeting was called to discuss the worsening clinical status and overall prognosis. Cardiology consultation offered right heart catheterization and the placement of an intraortic balloon pump (IABP). The right heart catheterization showed HR 130, aortic pressure 91/59, PA 55/39 mean 45, wedge 54, RA 50/49 mean 40, RV 55/39, SVR 750, PVR 1126, CO by Fick 3.20, CI by Fick 1.59. The patient was diagnosed with cardiogenic shock, and the IABP was set at 1:1 and a Shiley catheter was placed for urgent continuous veno-venous hemodialysis. The patient was weaned off of the phenyephrine and started on dobutamine, dopamine, and eventually epinephrine.

On the morning of the ninth hospital day, the cardiac care unit, heart failure, pulmonary, renal, and cardiothoracic surgery teams discussed the patient's case. Significant laboratory studies were: wbc 21 U/L, hemoglobin 7.9 g/dL, platelets 59 B/L, creatinine 2.5 umol/L, and AST 12217 U/L, and ALT 4060 U/L. Due to the rapid and progressive decline in cardiac function due to severe myocarditis, a decision was made to place a right ventricular assist device (RVAD) and a left ventricular assist device (LVAD), commonly called a BiVAD. The patient underwent surgery with the RVAD connecting the right atrium to the pulmonary arteries and the LVAD connecting the left ventricle to the aorta. A cardiac myocardial biopsy was also conducted during the surgical procedure. A collection of all lab results is included in Table 1.

Discussion

Often, myocarditis is an under-diagnosed medical condition. Its pathophysiology is marked by a triad: cardiac injury by inciting agent, immunologic response, and inflammation. Generally speaking 1/3rd of patients recover, 1/3rd experience permanent cardiac dysfunction, and 1/3rd deteriorate to either death or cardiac transplant.

Myocarditis' true incidence is most likely under represented. It has been postulated that up to 8.6% of sudden cardiac deaths may be attributable to myocarditis.[1] Up to 10% to 40% of what was thought to be idiopathic dilated cardiomyopathy in children may in fact be occult myocarditis.[2] As diagnostic techniques such as immuno-histochemistry, electron microscopy, and molecular proteomics advance inevitably the incidence of myocarditis will rise.

The diagnosis most often implies viral infection. The most common vectors of disease have thought to be enteroviruses such as coxsackie or adenovirus. However, any virus can cause myocarditis: cytomegalovirus, parvovirus, influenza, human immunodeficiency virus, hepatitis C, and Epstein-Barr virus have all been implicated. Furthermore, tricyclic antidepressants, clozapine, the smallpox vaccine, radiation, heat stroke, and hypothermia can all cause inflammation of cardiac tissue.

Clinically, the onset of symptoms can be insidious or rapid. Acutely, a viral prodrome often predominates with signs including fatigue, arthralgias, and fever. After this, cardiac manifestations may develop. In this particular case our patient presented with arrhythmia and heart block, which can be seen as the presenting symptom in 5% of cases.[3] Other symptoms such as chest pain and heart failure are often also present. Unfortunately, some patients may present with hemodynamic compromise and a fulminant picture.

Laboratory testing can include elevated ESR, WBC, or troponin. EKG findings are often non-specific and may range from subtle abnormalities to ST elevations. One study revealed that in the setting of an acute myocardial infarction and normal cardiac catheterization, 38% of patients were thought to have myocarditis.[4] Non-invasive techniques include transthoracic echocardiography in which regional wall motion abnormalities are typically more common than cardiac dilation. This is especially true in the acute to sub-acute period before cardiac remodeling has occurred. A less common used modality is indium-111 anti-myosin imaging. This is a nuclear medicine study in which anti-myosin antibodies are introduced, they bind to injured myocardium, and the results can then be quantified. The technique is excellent for detecting damage; however, distinguishing between a myocardial infarction and myocarditis may be difficult. In fact, the sensitivity is good at 85% to 100%, but the specificity is only 55%.[5] Another option

Table 1. Laboratory results

Infectious	Cardiovascular	Hepatology
Legionella Ag negative	Cholesterol 190	Hep A IgG/IgM negative
Lyme disease Ab 0.12 (negative)	HDL 33	Hep B IgG/IgM negative
Lyme PCR negative	LDL 120	Hep B core Ab negative
M.Pneumoniae IgM negative	Triglycerides 187	Hep B surface Ab negative
Ehrlichia Ab IgG/IgM negative		Hep C Ab negative
RPR negative	**Rheumatology**	Hep C PCR negative
HIV negative	RF 21 (wnl)	Alpha-1 antitryp quant 251 (high)
EBV IgM negative	ACE 21 (wnl)	Copper 47.7 (high)
EBV IgG positive	ANA negative	
EBV nuclear Ab positive	anti dsDNA 11 (wnl)	**Hematology**
CMV negative	ASM negative	Serotonin release negative
Herpes negative	C-ANCA negative	PLT factor 4 negative
RSV negative	P-ANCA negative	Iron 52 (wnl)
Varicella IgG Ab reactive		TIBC 252 (low)
VZV IgM 0.16 (negative)	**Endocrinology**	FeSat 24% (low-normal)
Coxsackie types negative	HgbA1C 5.7%	Ferritin 1085 (high)
Ent-virus PCR negative	TSH 0.65 (wnl)	
Influenza A+B negative	Cortisol 94	
CMV Ab IgM negative		
Toxoplasma negative		

is cardiac MRI which uses contrast kinetics to identify areas of damage and may be able to differentiate myocardial infarction from myocarditis. Epicardial predominance, a non-contiguous pattern, and involvement of the lateral wall are more common in myocarditis according to one study.[6]

The gold standard in the diagnosis of myocarditis is biopsy. For 20 years, the Dallas criteria have defined a positive biopsy as one that displays inflammatory cells plus necrosis. A borderline biopsy is one that has inflammatory cells but no necrosis.[7] However, this system is imperfect. The nature of myocarditis is such that it does not involve the entire myocardium. As such, even if one takes five biopsy specimens, the diagnosis will be missed 33% of the time.[8] Moreover, the disease often affects the lateral wall which is difficult to biopsy using current techniques. Detection of myocarditis via pathology can also be subject to observer differences. Furthermore, there are risks involved with the procedure such as vascular access issues, arrhythmias, and perforation.

Prognosis generally depends on the type of myocarditis. For example, giant cell myocarditis usually progresses quite rapidly, while other forms progress more subtly. As stated previously, patients may recover completely, sub-acutely progress to permanent cardiac dysfunction, or rapidly deteriorate to death or transplant. Generally, there is a 20% mortality at one year and 50% at four years. Predictors of death or requiring transplantation in the future include the presenting symptom of syncope or bundle branch block, an ejection fraction of <40%, and persistence of viral genome in the myocardium.[9] Unfortunately, our patient had two of these three predictors.

Regrettably, the treatment options for myocarditis leave much to be desired. The first steps are supportive therapies such as ACE inhibitors, diuretics, and beta blockers when clinically stable. The National Institutes of Health conducted a trial in which they randomized standard heart failure therapy versus steroids + azathioprine versus steroids + cyclosporine for six months. The results showed no difference in ejection fraction or mortality after four years.[10] There was some improvement during the acute treatment phase, but this was transient. Final recommendations included considering steroids in giant cell myocarditis or in hemodynamic compromise. In another trial,

interferon was used to treat 22 patients for six months. Virus was eliminated from myocardium in all 22 patients and 15 of 22 showed improvement in left ventricular systolic function.[11] The results were fairly promising and, consequently, have spurred an ongoing phase III trial. IVIG has been sought as therapy due to its effects on auto-antibodies. In 2003, IVIG was compared to placebo. Systolic function improved from 25% at baseline to 41% at six months, but there was no statistical difference in the two arms of the trial.[12] Currently, the most recognized treatments are supportive. Specifically, left ventricular assist devices have been shown to be beneficial in select patients. Indications for LVAD include: cardiac index < 2.0L/min/m2, central venous pressure or left atrial pressure >20, and urine output <20mL/hour despite maximal pharmacological therapy.[13] Furthermore, the disease may be so progressive that both right and left ventricular assist devices may be needed, such as in this case presented here. Indications for a BiVAD are renal, hepatic, and pulmonary dysfunction, seen with our patient.[14]

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