March Critical Care Case of the Month

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Chief Complaints

- Shortness of breath
- Worsening bilateral LE edema

History of Present Illness

A 53-year-old man with history of multiple myeloma and congestive heart failure presented to the emergency department with complaints of worsening shortness of breath and bilateral lower extremity edema for last 24 hours. In the last week, he has had dyspnea at rest as well as a productive cough with yellow sputum. He describes generalized malaise, loss of appetite, possible fever and notes new bilateral pitting edema below his knees. Per patient, he had flu-like symptoms one week ago and was treated empirically with oseltamivir.

Past Medical History

- Multiple myeloma-IgG kappa with calvarial and humeral metastases, ongoing treatment with cyclophosphamide, bortezomib and dexamethasone
- Community acquired pneumonia 2016, treated with oral antibiotics
- Heart failure with echo 10/2017 showing moderate concentric left ventricular hypertrophy, left ventricular ejection fraction 63%, borderline left atrial and right atrial dilatation, diastolic dysfunction, right ventricular systolic pressure estimated 25 mm Hg
- Hyperlipidemia
- Chronic kidney disease, stage III

Home Medications: Aspirin 81mg daily***,*** atorvastatin 80mg daily***,*** furosemide 10mg daily, calcium / Vitamin D supplement daily, oxycodone 5mg PRN, chemotherapy as above

Allergies: No known drug allergies

Social History:

- Construction worker, not currently working due to recent myeloma diagnosis
- Smoked one pack per day since age 16, recently quit with 30 pack-year history
- Drinks beer socially on weekends
- Married with 3 children

Family History: Mother with hypertension, uncle with multiple myeloma, daughter with rheumatoid arthritis

Review of Systems: Negative except per HPI

Physical Exam

- Vitals: T 39.3º C, BP 80/52, P121, R16, SpO2 93% on 2L
- General: Alert man, mildly dyspneic with speech
- Mouth: Nonicteric, moist oral mucosa, no oral erythema or exudates
- Neck: No cervical neck LAD but JVP to angle of jaw at 45 degrees
- Lungs: Bibasilar crackles with right basilar rhonchi, no wheezing
- Heart: Regular S1 and S2, tachycardic, no appreciable murmur or right ventricular heave
- Abdomen: Soft, normal active bowel sounds, no tendernesses, no hepatosplenomegaly
- Ext: Pitting edema to knees bilaterally, no cyanosis or clubbing, normal muscle bulk
- Neurologic: No focal abnormalities on neurologic exam

Laboratory Evaluation

- Complete blood count: WBC 15.9 (92% neutrophils), Hgb/Hct 8.8/27.1, Platelets 227
- Electrolytes: Na^+ 129, K^+ 4.0, Cl^- 100, CO2 18, blood urea nitrogen 42, creatinine 1.99 (baseline Cr 1.55)
- Liver: AST 35, ALT 46, total bilirubin1.7, alkaline phosphatase 237, total protein 7.4, albumin 2.
- Others: troponin 0.64, brain naturetic peptide 4569, venous lactate 2.6

Chest X-ray

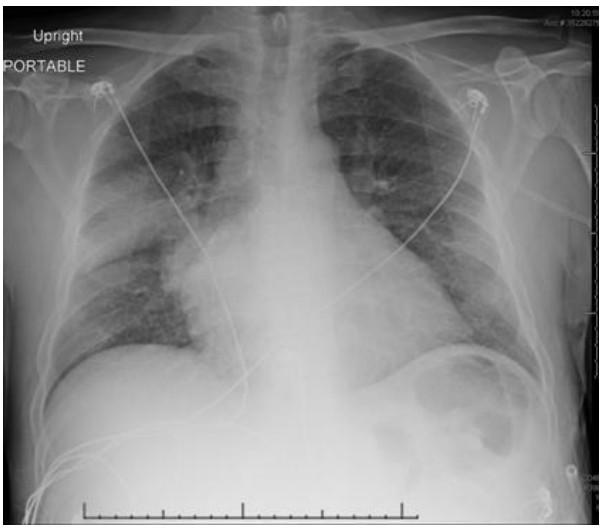

Figure 1. Admission chest x-ray.

Thoracic CT (2 views)

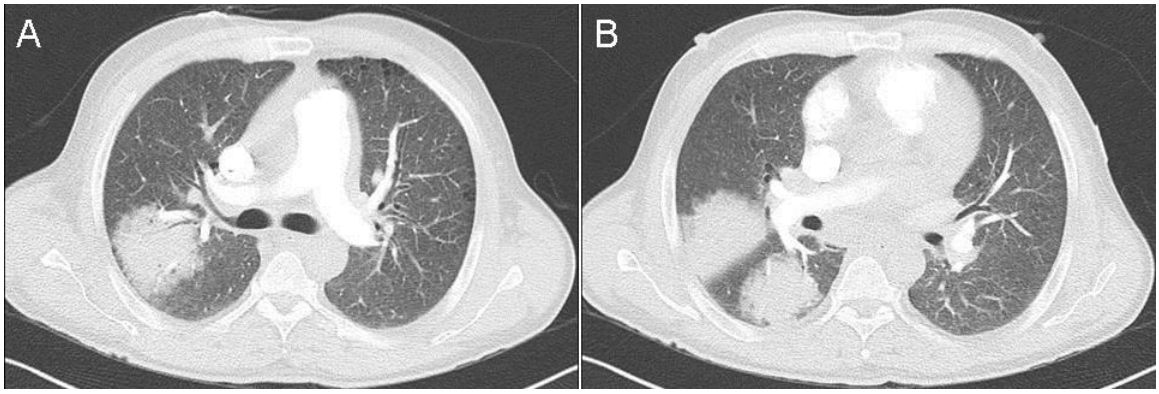

Figure 2. Representative images from the thoracic CT scan in lung windows.

What is ***most likely etiology*** of CXR and thoracic CT findings?

1. Coccidioidomycosis pneumonia
2. Pulmonary edema
3. Pulmonary embolism with infarcts
4. *Staphylococcus aureus* pneumonia
5. *Streptococcus pneumoniae* infection

Correct!
5. Streptococcus pneumoniae infection

The thoracic CT shows right upper lobe and right lower lobe consolidations most compatible with pneumonia as well as centrilobular and paraseptal emphysema. Patients with multiple myeloma are at increased risk of infection because of impaired plasma cell function with insufficient antibody function, impaired lymphocyte function, and potentially chemotherapy induced neutropenia. Streptococcus pneumoniae, Haemophilus influenza and Escherichia coli are the most common organisms typically causing pneumonia or urinary tract infections. Vaccination is recommended for influenza and pneumococcal disease even though the antibody response may be reduced in multiple myeloma patients.

Two ECGs were performed several hours apart (Figure 3).

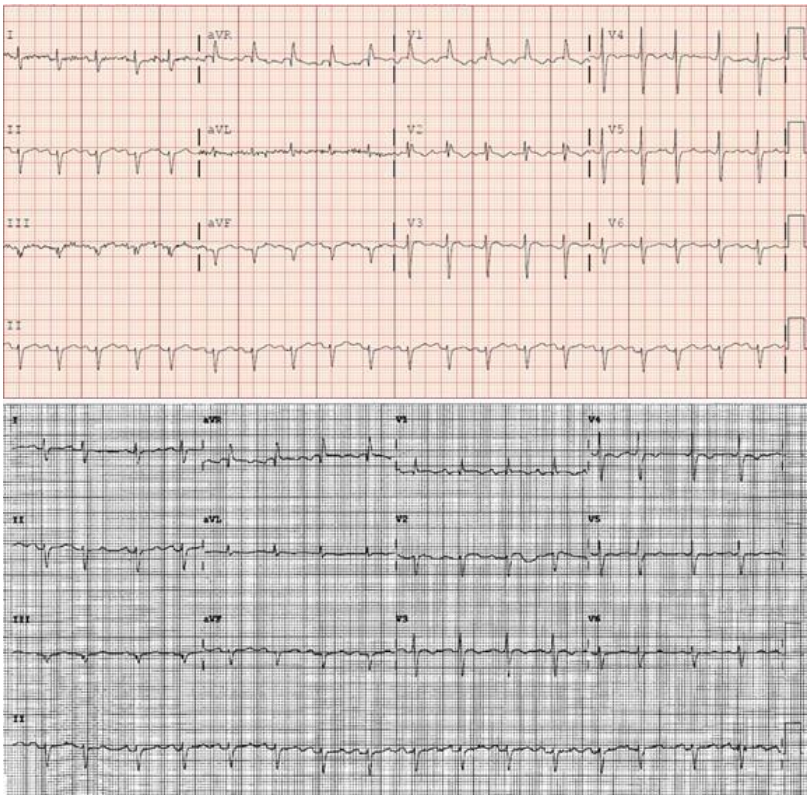

Figure 3. Electrocardiograms performed shortly after admission.

What is/are the ***significant finding(s)*** on these ECGs**?**

1. Atrial fibrillation
2. Left ventricular hypertrophy
3. Right bundle branch block
4. Right ventricular hypertrophy
5. All of the above

Correct!
4. Right ventricular hypertrophy (RVH)

This ECG meets criteria for RVH with right axis deviation, dominant R wave in V1, Dominant S wave in V5 and V6.

Criteria for RVH (1):

- Right axis deviation of +110° or more.
- Dominant R wave in V1 (> 7mm tall or R/S ratio > 1).
- Dominant S wave in V5 or V6 (> 7mm deep or R/S ratio < 1).
- *QRS duration < 120ms (Changes not due to RBBB).*

Some common causes of RVH include pulmonary hypertension, mitral stenosis, pulmonary embolism, cor pulmonale, and amyloidosis. It can also be a sequela of congenital heart disease, such as tetralogy of Fallot or pulmonary stenosis.

The ECGs do not show left ventricular hypertrophy (LVH). Criteria for LVH are numerous, but the most commonly used is the Sokolov-Lyon criteria (S wave in V1 plus R wave in V5-V6 >35mm) (2).

The ECGs show a normal sinus rhythm / tachycardia.

An echocardiogram was performed (Figure 4).

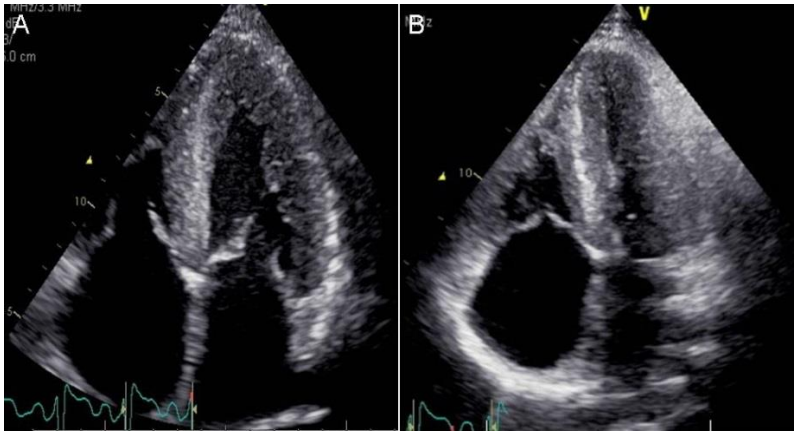

Figure 4. Representative apical 4 chamber echocardiographic views of the heart (diastole on the left and systole on the right).

What does ***echo most likely show***?

1. Heart failure with reduced ejection fraction from ischemic heart disease
2. Infiltrative cardiomyopathy from amyloid disease
3. Isolated biatrial enlargement
4. Left ventricular hypertrophy from hypertension
5. Pulmonary hypertension with dilated right ventricle

Correct!
2. Infiltrative cardiomyopathy from amyloid disease

The echocardiogram shows thickening of both LV (>12 mm) and RV (>5 mm) walls, and enlarged atria. The patient was noted on echo in October 2017 to have grade 3 diastolic dysfunction all of which suggest a restrictive cardiomyopathy. Restrictive cardiomyopathy can be caused by infiltrative diseases such as amyloidosis or sarcoidosis, noninfiltrative causes such as diabetes, storage diseases such as hemochromatosis or endomyocardial disease such as carcinoid heart disease. Given this patient's history of multiple myeloma, amyloid cardiomyopathy is most likely. Symptomatic amyloid is seen in about 15% of patients with multiple myeloma, and about 30% of patients with multiple myeloma have clinically occult amyloidosis (3).

Amyloid cardiomyopathy causes ventricular thickening from infiltrating amyloid fibrils, not myocyte hypertrophy. LV wall thickness greater than 12mm (6-10mm is normal) in the absence of hypertension should prompt work up for cardiac amyloid particularly with diastolic dysfunction. Characteristic 'speckling' pattern has low sensitivity and specificity. The LVEF is usually preserved, but the cardiac output is low due to decreased ventricular volume. This patient had a narrow pulse pressure on presentation likely from low stroke volume causing decreased cardiac output.

What is ***best method for diagnosing*** cardiac amyloid disease?

1. 99m Technetium pyrophosphate scan
2. Endomyocardial biopsy
3. Fat pad biopsy with echocardiogram findings consistent with amyloid disease
4. Right heart catherization
5. Serum free kappa / lambda light chain ratio

Correct!
2. Endomyocardial biopsy

Endomyocardial biopsy is the gold standard for diagnosis of cardiac amyloid (3). Risk of this procedure is right ventricular perforation leading to cardiac tamponade which is rare. Fat pad biopsy is 60-80% sensitive in AL amyloid so that a negative fat pad biopsy does not rule out amyloid disease. When suspecting amyloid disease, typical work up starts with serum and urine immunofixation and serum free light chain ratio. If these are normal, there is high negative predictive value in ruling out diagnosis of the most common forms of amyloid. Lastly, technetium pyrophosphate scan can be used to determine if there is uptake in the myocardium. A bone marrow biopsy may also be needed to confirm and determine the plasma cell clone.

What ***medications are relatively contraindicated*** in the treatment of amyloid heart failure?

1. Angiotensin-converting enzyme inhibitors
2. Loop diuretics and aldosterone antagonists with sodium restriction
3. Nondihydropyridine calcium channel blockers and beta blockers
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

Beta blockers are relatively contraindicated and nondihydropyridine calcium channel blockers are contraindicated mainly because of the decrease in heart rate (3). The heart rate is the only mechanism that maintains cardiac output given the already decreased stroke volume from the restrictive cardiomyopathy. Nondihydropyridine calcium channel blockers are contraindicated also because this drug binds to amyloid fibrils with risk of hypotension and syncope (3). Angiotensin converting enzymes are also relatively contraindicated because these drugs may lower blood pressure and significantly increase the already existing risk for orthostatic hypotension (3).

Amyloid cardiomyopathy is treated with sodium restriction and diuretics which is challenging with restrictive cardiomyopathies. Typically, a combination of loop diuretics and an aldosterone antagonist is most effective. Beta blockers may need to be used for rate control in atrial fibrillation. Anticoagulation needs to be considered even with normal sinus rhythm with poor atrial function and atrial fibrillation given the high risk of thromboembolic complications. Defibrillators are controversial but may be warranted in certain situations.

How do you ***treat primary cardiac amyloidosis***?

1. Bortezomib / cyclophosphamide / dexamethasone
2. Amphotericin
3. The same chemotherapy agents as initial multiple myeloma
4. 1 and 3
5. All of the above

Correct!
1. Bortezomib / cyclophosphamide / dexamethasone
3. The same chemotherapeutic agents as initial multiple myeloma
4. 1 and 3

The initial treatment of primary amyloidosis is the same as the initial treatment of multiple myeloma which is the combination of bortezomib, cyclophosphamide and dexamethasone (3). The goal is to reduce the neoplastic or abnormal plasma cell clone. Bortezomib is a proteasome inhibitor and cyclophosphamide is an alkylating agent. Survival in amyloidosis correlates with response to treatment. Serum N-terminal pro-BNP is a useful prognostic biomarker in cardiac amyloidosis.

Future therapies include an amyloid-directed monoclonal antibody that is designed to remove amyloid fibrils from the affected organs with ongoing phase 2b and phase 3 clinical trials. There is also an anti-SAP antibody (SAP is a protein that stabilizes amyloid fibrils) studied in a pilot trial with some patients having dramatic reversal of liver amyloid deposition leading to removal of the amyloid rather than just preventing further deposition.

References

1. Burns E. Right ventricular hypertrophy. Life in the Fast Lane. March 18, 2017. Available at: https://lifeinthefastlane.com/ecg-library/basics/right-ventricular-hypertrophy/ (accessed 2/27/18).
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3. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. Cleve Clin J Med. 2017 Dec;84(12 Suppl 3):12-26. [CrossRef] [PubMed]