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Diabetic Cardiomyopathy: Understanding the Independent Relationship Between Diabetes and Heart Failure.

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Introduction

Type 2 diabetes mellitus (DM) and heart failure (HF) are common chronic disorders that affect 29 million and 6.5 million Americans respectively[1]. While both often occur individually, there is an increase rate of the two diseases occurring concomitantly. It is estimated that 19-26% of patients with DM having clinically significant HF[2] and 10-47% of patients with HF having evidence of DM[1], both independent of other risk factors. This association between DM and HF is well documented, but the evidence supporting diabetic cardiomyopathy is less understood. This is due to the presence of other comorbid conditions such as hypertension (HTN) and coronary artery disease (CAD), both of which are independently associated with the development of HF[3].

Currently, Diabetic Cardiomyopathy (DCM) is defined as a clinical condition of ventricular dysfunction that occurs in the absence of significant CAD, HTN, or valvular disorders in a patient with DM[1,2]. This idea of a primary DM induced HF is important because it impacts the treatment of DM both independent and in the absence of CAD, HTN, or valvular disorders.

Case Report

History: A 34-year-old African American female with a past medical history of type 2 diabetes was admitted to our hospital from an outside emergency department due to anemia. History was obtained from the patient and her partner who was at the bedside. The patient reported feeling increasing malaise and lower extremity edema for 1 month with associated shortness of breath and chest pain (CP). She described the CP as a substernal pressure and like someone was “sitting on her chest.” She also complained of orthopnea and heartburn when lying flat, a dry cough that was now productive of white sputum, and sinus congestion. She denied any nausea, vomiting, diarrhea, constipation or abdominal pain, but did have 1 episode of posttussive emesis. She had previously been worked up for anemia without any diagnosis being made. She denied any history of epistaxis, menorrhagia, or melena. Blood sugars had been uncontrolled recently and were running 200-500 on her glucometer due losing her insurance and no longer having a primary care physician.

Past Medical History: Type 2 Diabetes, Hypertension, Hyperlipidemia.

Family History: Sickle Cell Trait

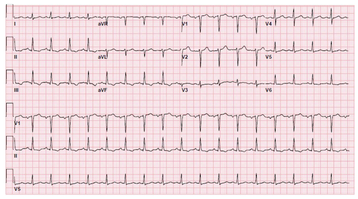
Medications: Atorvastatin, Hydrochlorothiazide, Insulin Levemir and Novolog, and Gabapentin.

Vital Signs: BP 184/91, HR 120, RR 20, T 37.1C, SpO2 96% RA, BMI 38.61

Physical Exam: On exam, the patient was an awake and alert obese female in mild distress. She had crackles noted in the lower lung lobes bilaterally and a tachycardic heartrate with a grade 2/6 systolic murmur. Jugular venous pulse was elevated. The abdomen was soft, nontender, and nondistended. The lower extremities were tense and edematous with nonpitting edema. Small purple lesions were scattered over the lower extremities.

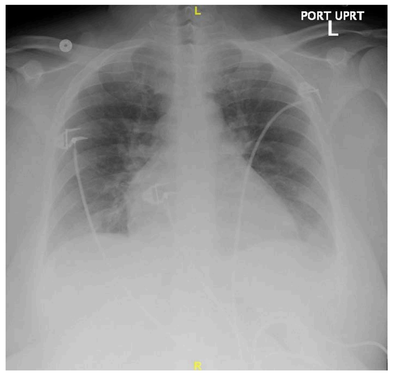
Labs:

- **CBC:** WBC 7.87, Hgb 7.1L, Hct 26.5L, Plts 422H
- **CMP:** Na^+ 137, K^+ 3.7, Cl^- 108H, CO_2 24, BUN 11, Cr 1.05, Gluc 322H, Ca^{2+} 8.0L, T_{Bili} 0.2, AST 42H, ALT 41, AlkPhos 186H, $T_{Protein}$ 5.6L, Albumin 1.9L, Mg^{2+} 1.8.
- **Troponin I:** 0.132H
- **Hemoglobin A1C:** 13.9H
- **D-Dimer:** 1.27H
- **Respiratory Virus Panel:** Negative

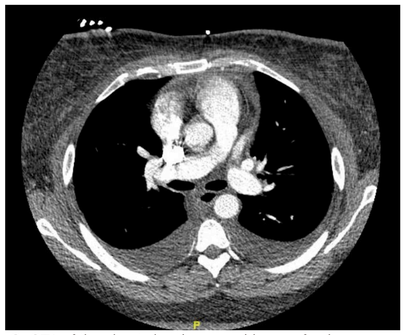


A. EKG from admission showing sinus tachycardia (Rate 108) with nonspecific T wave abnormalities.

Figures



B. Initial CXR showing no evidence of acute cardiopulmonary disease.



C. CTA of the chest showing no evidence of pulmonary embolism or suspicious lymphadenopathy. Small bilateral pleural effusions with associated atelectasis.

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LEFT VENTRICLE:
- The left ventricle is normal in size.
- The ejection fraction is calculated to be 51 % evaluated by
biplane method of disks.
- The LV wall thickness was mildly increased.
- The basal inferoseptal and mid inferoseptal left ventricular wall
segments are hypokinetic. The basal inferior and mid inferior left
ventricular wall segments are akinetic. .
- Features were consistent with a pseudonormal left ventricular
filling pattern, with concomitant abnormal relaxation and
increased filling pressure (grade 2 diastolic dysfunction).
RIGHT VENTRICLE:
- Right ventricle is normal in size.
- The right ventricular systolic function is normal.
- Pulmonary artery pressure is mildly increased.
- RVSP: 45 mmHg.
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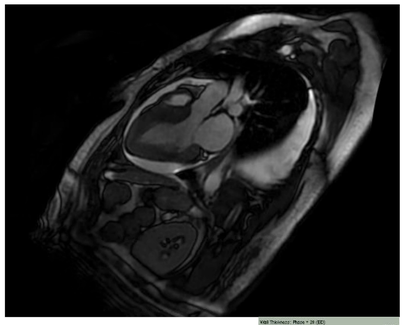
D. ECHO report documenting a normal size left ventricle with an ejection fraction of 51%. There is mild thickening of the left wall. Segments of the basal inferoseptal and mid inferoseptal walls are hypokinetic. Segments of the basal inferior and mid inferior left ventricular wall are akinetic. Findings were consistent with a pseudonormal left ventricular filling pattern, with concomitant abnormal relaxation and increased filling pressure (Grade 2 Diastolic Dysfunction).
There was normal ventricular size and function of the right ventricle.



E. Cardiac MRI showing a decreased ejection fraction and focal areas of hypokinesis involving the basal inferoseptum and mid inferoseptal myocardium with thickening of the wall. There are areas suggestive of fibrosis/scarring. No findings of sarcoidosis or infiltrative cardiomyopathy.

Case Conclusion

During her admission, the patient underwent extensive evaluation for her complaint of malaise. Her ECHO (Figure D) showed evidence of heart failure with abnormal ventricular relaxation, which was consistent with the fibrosis/scarring noted on her cardiac MRI (Figure E). The differential diagnoses were whether the cardiomyopathy was primarily related to her DM or due to ischemia. Due to the elevated troponin, the patient eventually underwent a coronary catheterization which showed partial occlusion of the right coronary artery. While this finding was evidence of the presence of CAD, discussion amongst the care team felt that the cardiomyopathy was primarily related to the patients long standing and markedly uncontrolled DM, while this incident of acute decompensation was likely related to acute ischemia.

Final Diagnosis: Diabetic Cardiomyopathy

Discussion

The development of DCM is related to the effects of DM systemically, on the myocardium, and directly on cardiomyocytes[3]. Hyperglycemia, hyperinsulinemia, and insulin resistance are the major contributors to the pathogenesis of DCM, causing autonomic dysfunction, oxidative stress, and altered cellular metabolism (Figure F). This results in cardiac hypertrophy and fibrosis, dysregulation of the renin-angiotensin-aldosterone system (RAAS), and the formation of advanced glycation end products (AGEs), all of which contribute to the eventual development of HF[1,3]. Additionally, DM is also a major risk factor for CAD by increasing the arthogenicity of lipids and accelerating the formation atherosclerosis; therefore also contributing indirectly to the development of HF[1].

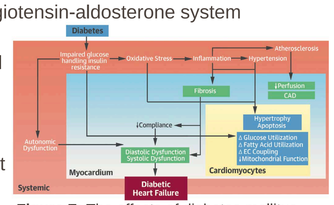


Figure F: The effects of diabetes mellitus systemically, on the myocardium, and on individual cardiomyocytes[3].

Functionally, one of the earliest manifestations of DCM is left ventricular hypertrophy (LVH), primarily affecting the ventricular septal and left posterior myocardial walls[4], along with associated diastolic dysfunction[5]. These early cardiac changes occur subclinically and are believed to be present in 40-75% of patients with DM[6]. This is important because cardiac damage and disease progression begin before patients ever develop clinical symptoms, which highlights the challenge of how to effectively identify and treat patients with DCM.

Multiple studies have sought to use markers and tests such as B-type natriuretic peptide (BNP), exercise stress testing, echocardiography, and nuclear imaging to identify patients with subclinical disease, but none have proved to have sufficient sensitivity or specificity[7,8]. As a result, an understanding and clinical awareness of diabetic cardiomyopathy by providers when managing diabetic patients is imperative. The UK Prospective Diabetes Study found that a 1% reduction in hemoglobin A_{1C} (HbA_{1C}) was associated with a 16% risk reduction for the development of HF[9]. In patients with diagnosed HF though, DM management had a more U-shaped effect, with the lowest mortality among patients with a with a HbA_{1C} of 7-8%[2].

Another important decision in the management of patients with DM is medication selection. Research has shown that SGLT-2 inhibitors are the most beneficial for DM patients both at risk of developing HF or with established HF, while GLP-1 receptor agonists are beneficial in establish HF[1]. Insulin, metformin, and sulfonylureas are acceptable alternatives and thiazolidinediones and dipeptidyl peptidase-4 inhibitors (DPP-4) are not recommended in patients at risk or with established HF[1].

Understanding the development of DCM and how best to identify and treat this condition is vital to improving patient morbidity and mortality.

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