Acute Heart Failure in Scleroderma Renal Crisis: A Case Study for Review of Cardiac Disease in Systemic Sclerosis

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Keywords

1. Case Presentation

A 59-year-old woman with a past medical history of asthma, recently-diagnosed breast cancer (stage 0) and diffuse systemic sclerosis (SSc) diagnosed 3 years prior -no known internal organ involvement-, presented with 8 days of worsening shortness of breath. She reported wheezing, chest tightness, fatigue, cough productive of clear sputum, and dyspnea on exertion. She had been seen in the emergency department (ED) two days earlier and was diagnosed with an acute asthma exacerbation. During that visit, she received nebulized albuterol and prednisone and was discharged home on oral methylprednisolone. However, her respiratory symptoms failed to improve, and she returned to the ED.

On admission, the patient reported that her shortness of breath was becoming progressively worse. She denied any fever, chills, calf pain, orthopnea, paroxysmal nocturnal dyspnea, anxiety, lightheadedness, tingling, numbness, or palpitations. She had no additional past medical history. Her surgical history consisted of bilateral cataract removal and uterine artery embolization for fibroids. Her home medications included Breo (fluticasone-furoate and vilanterol), triamcinolone 0.1% topical cream, and albuterol. Her family history was non-contributory. The patient denied any current or history of smoking, drinking alcohol, or using drugs. She denied any recent travel.

On examination, the patient's BMI was 21.4 kg/m^2. Her temperature was 97.8 degrees Fahrenheit, heart rate 90 beats per minute, respiratory rate 20 breaths per minute, blood pressure 157/112, and oxygen saturation 98% on room air. The patient appeared dyspneic and spoke in short sentences. Her lung examination revealed moderate respiratory distress with accessory muscle use, decreased breath sounds bilaterally, and biphasic wheezes

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posteriorly. She was found to have multiple areas of hypopigmentation consistent with vitiligo as well as skin tightening over the dorsum of both hands, resulting in limited range of motion of her wrists and inability to make a fist bilaterally. She also had decreased strength of abduction at her shoulders, extension at her knees, and dorsiflexion at her ankles. Her lower extremity exam revealed 2+ pitting edema bilaterally with intact peripheral pulses. Her cardiac, abdominal, neurologic, and head and neck exams were normal.

Bloodwork on admission was significant for a first troponin I level of 2.56 ng/mL, brain natriuretic peptide (BNP) of 4271 pg/mL, and creatinine (Cr) of 1.07 mg/dL. See Table 1. Electrocardiogram (EKG) showed normal sinus rhythm and a rate of 90, with ST depression in leads II, aVF, V5, and V6 and T-wave inversions in leads II, aVF, and V3–V6. See Figure 1. Chest x-ray demonstrated an enlarged cardiac silhouette, with small bilateral pleural effusions and prominent pulmonary vascularity consistent with pulmonary edema. Chest CT was negative for a pulmonary embolism. Bedside echocardiogram showed dilated cardiomyopathy with severely decreased ejection fraction, bilateral B lines, and bilateral pleural effusions.

Given the concern for new onset heart failure in the setting of suspected Non-ST elevation myocardial infarction (NSTEMI), the patient was loaded with full dose aspirin and clopidogrel, initiated on heparin drip, furosemide, and admitted to the coronary care unit.

On day 2 of hospitalization, the patient underwent right and left cardiac catheterization, which revealed normal coronary arteries, severe left ventricular (LV) systolic dysfunction, moderate-to-severe mitral regurgitation (MR), and moderate pulmonary hypertension. Ventriculography demonstrated an ejection fraction (EF) of 10%. She underwent formal transthoracic echocardiography (TTE), which demonstrated mild LV dilation, LVEF of 20%, grade II diastolic dysfunction, left atrial (LA) dilation, mild MR, and mild tricuspid regurgitation (TR). See Figure 2. Laboratory data demonstrated a decreased second troponin I of 2.18. However, creatinine increased to 1.38.

- How would you further evaluate and manage this case?

- How could the diagnosis of cardiac disease in scleroderma have been identified earlier?

- What are considerations for best management of this case to improve outcomes in patients with SSc renal crisis and cardiac disease?

2. The Clinical Problem

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated multisystem connective tissue disorder. The iconic feature of SSc is progressive collagen deposition leading to cutaneous thickening. However, SSc also leads to dysregulated, dysfunctional, and excessive fibrotic tissue synthesis in the microvasculature, interstitium, and internal organs. The anatomical location and chronology of fibrosis can help to distinguish between diffuse cutaneous SSc and limited cutaneous SSc, also referred to as CREST syndrome (acronym for Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia) [1,2,3]. Common internal organs involved in both SSc types are the

gastrointestinal tract and the respiratory system. For example, limited SSc is associated with pulmonary vascular fibrosis and subsequent increased pulmonary vascular resistance, while interstitial lung disease (ILD) is an important comorbidity in diffuse SSc [1,4,5].

Despite the protean and overall poor prognosis associated with the cardiac manifestations seen in SSc, there are no guidelines for assessment, screening or management [6,7]. Hereby, we present a comprehensive review of the current literature on the acute and chronic cardiac manifestations of SSc and highlight the pathophysiology, diagnosis, and management of scleroderma cardiac disease.

3. Key Clinical Points

- Systemic sclerosis (SSc) is a multisystem disorder that is characterized by thickening of the skin due to fibrosis and microvascular changes. Visceral involvement is more frequent encountered in the diffuse cutaneous subtype of SSc. A thorough cardiac assessment is recommended even in asymptomatic patients.

- Cardiac manifestations include left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, right ventricular (RV) dysfunction, coronary artery disease, perimyocarditis, and conduction abnormalities leading to arrhythmias.

- Cardiac involvement in SSc is often clinically silent, leading to late detection, and associated with a poor prognosis.

- Laboratory evaluations include ESR, ANA, anti-topoisomerase I, anti-centromere, RNA polymerase III, and U3-RNP (fibrillarin).

- Screen for cardiac disease in patients with SSc at presentation and every year thereafter with Pro-brain natriuretic protein (Pro-BNP), electrocardiography, and Doppler Echo.

- Early intervention with nifedipine can improve cardiac function in SSc by minimizing vasospastic episodes and decreasing the risk of ischemia-reperfusion injury.

- While glucocorticoids are indicated for treating pericarditis and inflammatory myositis in SSc, the progression of the disease remains unchanged.

4. Pathophysiology

An autoimmune etiology for SSc disease is supported by the observation that patients with SSc have circulating autoantibodies, increased secretion of inflammatory cytokines, and immune cells detected in SSc tissue biopsies. Furthermore, familial clustering of SSc has identified non-HLA-linked genes and major histocompatibility loci alleles associated with SSc.

While extracellular matrix disorganization and fibrosis underlie the skin thickening characteristic of SSc, vascular insults play an important additional role in the pathophysiology of SSc cardiac disease. In early disease, inflammatory cells such as

leukocytes, monocytes, macrophages, and mast cells can be detected on organ biopsy. Non-inflammatory obliterative vasculopathy is often the pathology found in the heart, likely indicating late disease. Myocardial fibrosis and ischemia-reperfusion injury are reflected by arteriolar lesions with concentric intimal hypertrophy, luminal narrowing, and band necrosis. Reversible vasospasm of small coronary arteries and arterioles also plays a role in ischemia-reperfusion injury to cardiac tissues. Additionally, collagen, fibronectin, proteoglycans, and other structural macromolecules deposit and disrupt the cardiac architecture.

Secondary cardiac disease can develop due to ILD, pulmonary arterial hypertension (PAH), or kidney disease. In PAH, fibrosis of the pulmonary vessels and parenchyma increases the risk for right ventricular (RV) strain and heart failure in SSc [9]. RV function can also be affected by elevated pulmonary vascular pressures secondary to left ventricular (LV) dysfunction in SSc primary myocardial fibrosis [9]. In kidney disease, cardiac complications can be related to uremia from acute renal failure, which can cause pericarditis [16]. Additionally, elevated blood pressures in patients with SSc renal crisis (SRC), such as in malignant hypertension and hypertensive emergency, can cause acute pulmonary edema without fulminant LV failure. Acute systolic dysfunction in SSc most frequently manifests secondary to SRC, with blood pressures >150/90 mmHg in 90% of SRC cases, highlighting the central pathophysiologic role of the renin-angiotensin-aldosterone axis. Of note, systolic dysfunction is a more common finding in advanced SSc, with diastolic dysfunction and late stage systolic failure being more associated with progressive primary myocardial fibrosis. Severity of both systolic and diastolic dysfunction worsens with age, disease duration, and presence of SSc pulmonary complications [6,10,11].

5.   Strategies and Evidence

5.1.   Diagnosis and Evaluation

The most important screening tests for heart disease in SSc are BNP or pro-BNP, EKG, and tissue Doppler echocardiography. These tests should be completed at initial presentation and then yearly, alongside screening for PAH. Importantly, conventional echocardiography has a low sensitivity for preclinical SSc heart involvement; therefore, tissue Doppler imaging is recommended instead. Other evaluation modalities include cardiac magnetic resonance imaging (MRI), thallium perfusion studies, and single-photon emission CT. If heart abnormalities are identified, additional imaging can be obtained to evaluate more specific cardiac pathologies, including myocardial strain (via speckle-tracking echo), diffuse cardiac fibrosis (via diffuse fibrosis imaging cardiac MRI), and microangiopathy (via absolute perfusion cardiac MRI).

Evaluation can reveal primary cardiac involvement in SSc leading to LV systolic dysfunction, LV diastolic dysfunction, RV dysfunction, coronary artery disease, perimyocarditis, and arrhythmias. Furthermore, secondary cardiac involvement can also develop via PAH and subsequent RV strain. Since many types of cardiac involvement are identifiable in SSc, we highlight here diagnostic techniques for different cardiac manifestations of SSc.

5.1.1.   Secondary Cardiac Disease (Group 3 Pulmonary Hypertension)—

Pulmonary involvement is the leading cause of death in SSc. Pulmonary vascular disease, ILD, and RV dysfunction secondary to PAH are pulmonary manifestations in SSc that directly increase morbidity and mortality. BNP/proBNP/NT-proBNP levels can be used to define ventricular stretch and evaluate RV dysfunction due to group 3 PAH [12]. In SSc patients with secondary RV dysfunction, hyponatremia indicates a poor prognosis [13], similar to standard heart failure guidelines. Predictive outcomes in PAH have been shown to be linked to RV function. Specifically, decreased RV afterload and stroke volume index are associated with decreased survival in SSc patients with RV disease secondary to PAH, while standard cardiac index and right atrial pressure measurement have not been shown to independently predict survival [14].

5.1.2.   LV Dysfunction—

Multiple studies have demonstrated the high prevalence of acute LV failure in SRC, with a rate of 25–56% [15,16,17,18], while systolic dysfunction is one of the rarest findings in SSc with a prevalence of 1.4–5.4% and the rate of LV hypertrophy/diastolic dysfunction ranges between 17.7%–35% [19]. When clinically silent, LV dysfunction can be detected with Doppler echo, cardiac MRI, and pro-BNP or BNP. In SRC, renal vascular involvement leads to the development of malignant hypertension, rising creatinine, and oliguric acute renal failure. Patients who develop a reno-cardiac syndrome have increased risk of mortality, particularly if they develop LV diastolic dysfunction, and reno-cardiac syndrome is more strongly correlated with mortality than PAH without cardiac disease [20]. Kidney injury can lead to cardiac changes due to paracrine effects, metabolic acidosis, and electrolyte abnormalities. In addition, progressive sodium retention can predispose the patient to atherosclerosis, hypertension, and subsequent ventricular fibrosis. Furthermore, valvular calcification and carnitine deficiency in patients on hemodialysis can lead to the development of reduced LVEF. Given this, patients with SSc and rising creatinine should be screened for LV diastolic dysfunction in addition to SRC through BNP, proBNP, and NT-proBNP measurements and tissue Doppler imaging [19,20].

5.1.3.   Primary RV Dysfunction—

RV dysfunction can be due to primary cardiac involvement or secondary to PAH (discussed above as group 3 PAH). Primary RV dysfunction can only be diagnosed after ruling out PAH with invasive hemodynamic testing after initially non-invasive measures such as echocardiography and pulmonary function tests. Once primary cardiac involvement is determined in SSc patients, specific right heart assessment guidelines should be followed for further evaluation [21]. Abnormalities in RV diastolic dysfunction can be defined initially through BNP/proBNP/NT-proBNP testing and tissue Doppler imaging. Prospective case evaluation of SSc patients with primary RV dysfunction indicated that RVEF was correlated with LVEF and peak filling rate, but not PAH [22]. Therefore, primary RV dysfunction is not usually isolated and is associated with further intrinsic myocardial injury.

5.1.4.   Coronary Artery Disease—

Microvascular coronary artery disease in SSc can be driven by obstructive vasculopathy intrinsic to the disease pathophysiology or secondary to renal disease in SRC. In either case, signs and symptoms are often similar to those in myocardial ischemia, including chest pain and dyspnea. To quantify microvascular coronary

artery disease, nuclear myocardial perfusion imaging or cardiac MRI can be utilized. Coronary CT can be used to screen cases of SSc with subclinical cardiac disease for macrovascular disease, which is more often epicardial. On histopathology, artherosclerotic disease in SSc coronary artery disease can be differentiated from atherosclerosis by the involvement of the subendothelial layer and the presence of hemosiderin deposits [23].

5.1.5.   Perimyocarditis (with Pericardial Effusion)—Perimyocardial disease in patients with SSc is often clinically silent, with symptoms reported in only 5–16% of patients [24]. However, when clinically symptomatic, perimyocarditis can lead to acute pericarditis, pericardial effusion, constrictive pericarditis, and cardiac tamponade. It is often difficult to differentiate between constrictive pericarditis and restrictive cardiac disease from intrinsic myocardial pathology. As such, clinicians should be cautious when considering pericardiocentesis, with close evaluation of ventricular function through Doppler echocardiography alongside evaluation for cardiac tamponade. Furthermore, cardiac MRI and endomyocardial biopsy can be utilized to further define constrictive versus restrictive disease in SSc patients.

5.1.6.   Arrhythmia—The subsequent transient myocardial ischemia from coronary vasospasm can drive cardiac remodeling that in turn leads to conduction system abnormalities. Ventricular ectopic beats, ventricular tachycardia, late ventricular potentials, bradyarrhythmias, and supraventricular arrhythmias have all been described in association with SSc [25,26,27]. Non-segmental perfusion defects can be evaluated through myocardial stress perfusion cardiac MRI. In addition, patients with SSc and palpitations should be further evaluated through holter monitor study.

5.2.   Laboratory Testing

Important evaluation measures include ESR, ANA, and autoantibody titers. Anti-topoisomerase I (Anti-Scl-7) and anti-centromere antibodies are the most common autoantibodies present in systemic sclerosis. Anti-centromere autoantibodies are more associated with CREST syndrome, while anti-topoisomerase I, RNA polymerase III, and U3-RNP (fibrillarin) are more associated with diffuse SSc.

While auto-antibodies specific to SSc cardiac disease have not yet been identified, a recent study reported that select anti-Ro subtype autoantibodies (against anti-Ro52 and anti-Ro60) were identifiable in patients prior to SRC [28]. These data suggest that select autoantibodies may be useful in future laboratory testing to stratify patients with an increased risk of developing SRC, and potentially SSc cardiac disease as well.

5.3.   Management

Smoking cessation is essential counseling for all patients with SSc, especially to decrease risk of vasospasm in patients with preclinical cardiac disease and to reduce the incidence of ischemia-reperfusion injury. Early intervention with calcium channel blockers (CCBs) improves cardiac perfusion and ventricular function [29]. The underlying benefit likely stems from minimizing vasospasm that drives ischemia-reperfusion injury. As such, nifedipine can be utilized early in disease even in patients without peripheral vascular

disease. Nifedipine is also useful for treating Raynaud's phenomenon, as in this patient. With nifedipine and other CCBs, it is important to monitor for reflex tachycardia and peripheral edema.

Other medications with potential benefit in primary cardiac manifestations of SSc may include losartan and ACE inhibitors, to better control hypertension, and nitroglycerin paste, to prevent vascular spasm. Patients with SRC have a robust clinical response to treatment with ACE inhibitors [6,30]. Prostacyclin, bosentan, and sildenafil may improve cardiopulmonary hemodynamics in patients with cardiac manifestations of SSc secondary to PAH.

Beyond these general treatment approaches, specific management approaches should be considered for different primary cardiac manifestations of SSc.

5.3.1.   Management of LV Dysfunction—Since a reno-cardiac axis of disease can often underlie LV dysfunction, treatment of SRC includes ACE inhibitors and ARBs. Improving serum creatinine and hypertension not only treat renal disease, but also to decrease sodium retention and therefore inhibit cardiac remodeling. Beta blockers should be used cautiously, especially in SSc patients with Raynaud's. If a beta blocker is to be used, carvedilol is preferred for rate control in patients with SSc cardiac disease because it offers both rate control and vasodilatory effects. Evidence supports the use of CCBs (e.g. nifedipine) to improve cardiac perfusion and LV function [22], especially if microvascular ischemic disease is present. Similar to in non-SSc ischemic cardiac disease, digoxin and diuretics can be utilized for symptomatic treatment but have not been demonstrated to treat the underlying pathophysiologic disease of SSc LV dysfunction.

5.3.2.   Management of Coronary Artery Disease—Similar to atherosclerosis management, the use of statins and control of blood pressure and diabetes can minimize the risk of ischemic cardiac disease secondary to coronary artery disease. Ranolazine can be considered for angina treatment. CCBs and ACEi/ARBs should be utilized to treat microvascular disease. If macrovascular disease is observed, then coronary stenting, along with statins and standard CAD management, should be considered.

5.3.3.   Management of Perimyocarditis (with Pericardial Effusion)—Pericardial effusion in perimyocarditis should only be treated if symptoms develop. These patients should be closely evaluated for PAH. Pericardiocentesis is relatively contraindicated in patients with significant grade 3 PAH. For acute pericarditis, cyclophosphamide and IV pulse steroids have been utilized. Importantly, glucocorticoids have no efficacy in slowing the progression of SSc, but are indicated for inflammatory myositis or pericarditis. It is important to use glucocorticoids cautiously because retrospective studies have shown an association between corticosteroids and SRC [31]. If patients develop heart failure, treat based on standard heart failure guidelines.

5.3.4.   Management of Cardiac Arrhythmia—For patients with conduction abnormalities, standard electrophysiological studies and pacemaker guidelines should be utilized. Centrally-acting CCBs, such as diltiazem and verapamil, are preferred for rate

control. Although beta blockers are also important for rate control in arrhythmia, they should generally be avoided in patients with Raynaud's disease. On the other hand, a combination of metoprolol and a CCB such as felodipin may be effective in treating Raynaud's symptoms [32]. Ablation and AICD implantation should be strongly considered in patients with reduced LVEF and/or inducible ventricular tachycardia.

5.4. Guidelines from Professional Societies

Cardiac complications of SSc are not currently included in the diagnostic and classification guidelines of the American College of Rheumatology (ACR) or the European League Against Rheumatism (EULAR). However, complications of target organ cardiac dysfunction, including acute heart failure and pericarditis, are included in the classification criteria for SRC [33,34].

5.5. Areas of Uncertainty

- Early detection of cardiac disease and preventative intervention of progression to clinical disease may be beneficial, but it is unclear how early intervention in preclinical disease should occur.

- Vasospasm and fibrosis play a pathophysiologic role in cardiac disease of SSc, but anti-fibrotic pharmacotherapy has not yet been robustly studied for cardiac disease treatment, especially given the cardiac side effects of some antifibrotic medications.

- Can select autoantibodies be utilized to define an increased risk for SSc cardiac disease?

- New imaging modalities, such as thallium scintigraphy and single-photon emission CT thallium have shown promise to identify cardiac disease at a larger prevalence than previous SSc cardiac studies, but their utilization as a screening tool for SSc cardiac disease has not yet been rigorously studied.

- The use of glucocorticoids is commonplace, but retrospective studies have shown an association between scleroderma renal crisis and glucocorticoid use. It is still unclear if further prospective cohort studies will define a similar association, and whether other pharmaceutical options for acute treatment of SSc cutaneous disease and acute pericardial disease will emerge.

- Since cardiac complications of SSc are not currently included in the ACR/ EULAR classification guidelines, likely due to insufficient evidence for subclassification, studies into defining prognosis, improved monitoring, and methods to increase survival in patients with cardiac complications of SSc are necessary.

6.   Conclusions and Recommendations

The patient described in the vignette has scleroderma renal crisis and secondary acute cardiac decompensation. Rheumatology was consulted, and the patient was initiated on captopril while still in the coronary care unit. Subsequently, her blood pressure normalized

to 107/66 and serum creatinine downtrended to 1.21. The patient was adequately diuresed with furosemide, and her acute heart failure symptoms improved over four to five days. She was discharged on enalapril, nifedipine, and rosuvastatin with additional guideline-directed therapy for heart failure with reduced ejection fraction (furosemide and metoprolol). She was also fitted for an external, wearable defibrillator prior to discharge. Follow-up TTE at two months post discharge showed notable heart failure improvement, with her ejection fraction increased from 20% to 50–55%.

This case highlights that although there is no cure available for the cardiac manifestations of SSc, there are options for early detection and management. The majority of scleroderma cardiac complications, such as LV systolic dysfunction and congestive heart failure, are related to the chronic progressive fibrosis of the myocardium and microvasculature. However, acute LV insufficiency in the setting of SSc (as seen in the presented case) is a more commonly-seen association with SRC [8,10]. With early intervention and use of ACE inhibitors, along with symptom-guided SSc therapies, patients can potentially have recognizable improvement in cardiac function and quality of life.

Acknowledgements

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Figure 1.
EKG on admission ST depression in leads II, aVF, V5, and V6 and T-wave inversions II, aVF, and V3–V6
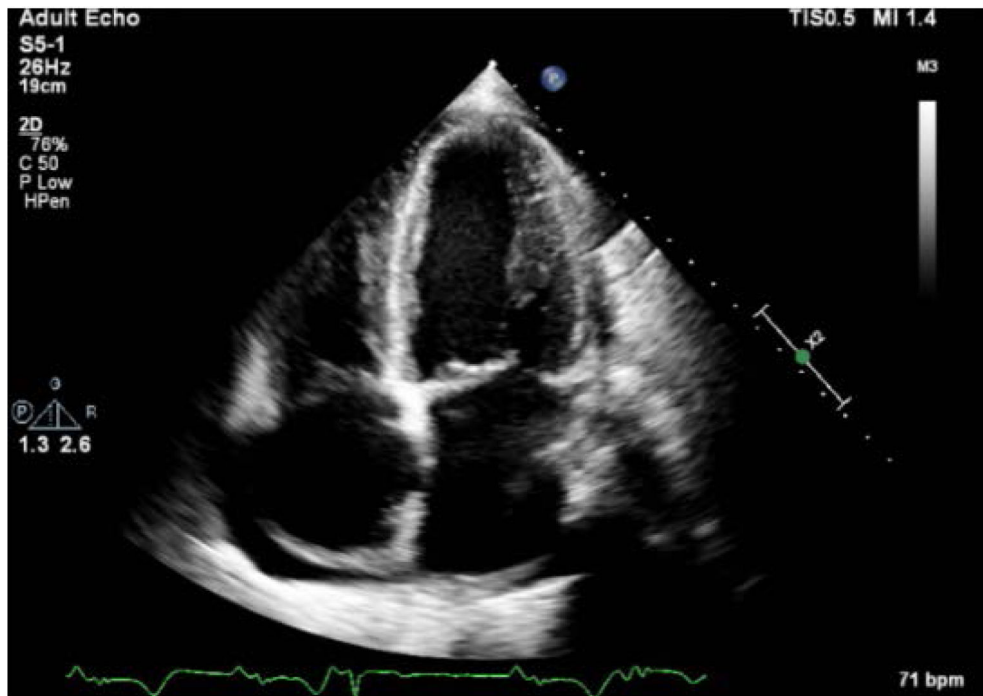
Figure 2.
Transthoracic echocardiogram demonstrating poor ejection fraction and pericardial effusion

Table 1.

Laboratory data

Serum	Patient	Reference Range
WBC (K/uL)	7.27	3.50–10.80
RBC (M/uL)	3.66	4.10–5.40
Hemoglobin (g/dL)	11.9	12.0–16.0
Hematocrit (%)	36.7	37.0–47.0
MCV (fL)	100.4	78.0–98.0
Platelets (K/uL)	298	130–400
Sodium (mmol/L)	133	136–145
Potassium (mmol/L)	4.3	3.5–5.1
Chloride (mmol/L)	101	98–107
CO_2 (mmol/L)	18	21–31
BUN (mg/dL)	33	7–25
Creatinine (mg/dL)	1.07	0.70–1.30
Calcium (mg/dL)	9.5	8.2–10.0
Total Protein (g/dL)	8.0	6.0–8.3
Albumin (g/dL)	4.00	3.50–5.70
AST (u/L)	27	13–39
ALT (u/L)	23	7–52
Alk Phos (U/L)	55	34–104
Total Bilirubin (mg/dL)	0.70	0.30–1.00
Glucose (mg/dL)	100	70–99
Mg (mg/dL)	2.3	1.9–2.7
Phos (mg/dL)	4.1	2.5–5.0
aPTT (sec)	28.1	25.4–38.6
PT (sec)	12.6	10.5–13.1
Cholesterol (mg/dL)	240	<=200
Triglycerides (mg/dL)	222	<=200
HDL (mg/dL)	41	>=40
LDL (mg/dL)	155	<=159
Hemoglobin Ale (mmol/mol)	4.9	4.0–5.6
TSH (uIU/L)	1.54	0.35–4.70
Thyroxine (ug/dL)	6.6	5.2–10.5
BNP (pg/mL)	4271	<125