A 52-year-old woman presented to her local emergency department with acute-onset, nonradiating 9/10 abdominal, and right flank pain that started the day before. She denied any specific precipitating event and endorsed additional symptoms of progressive abdominal distention over the past 1 month, lower-extremity edema over the past 5 months, mild shortness of breath and dyspnea on exertion over the past 5 months, and intermittent palpitations over the past 6 years. Review of systems was otherwise negative. Her medical history consisted of only iron deficiency anemia and hyperthyroidism, treated with occasional use of herbal supplements. Her only prescribed medication was methimazole, which she had self-discontinued without physician follow-up. She acknowledged occasional alcohol consumption but denied tobacco or recreational drug use. Family history was notable for hyperthyroidism in a sister and hypertension with hypertensive nephropathy in an uncle. There was no family history of arrhythmias, premature coronary artery disease, or liver dysfunction. On physical examination, she was afebrile, saturating 87% on room air, blood pressure of 115/61, heart rate (HR) 143 beats per minute (bpm) and an irregularly irregular rhythm, 3/6 systolic murmur appreciated at the right lower sternal border, jugular venous pulse (JVP) at ear lobe with the bed at 30° with prominent cv wave, hyperdynamic precordium, clear lung fields, symmetric bilateral 2+ lower- extremity edema, diffusely enlarged nontender thyroid, bilateral exophthalmos, bilateral upper- extremity tremors, brisk reflexes throughout, soft abdomen with tenderness in all quadrants but without rebound or guarding, positive fluid wave, and hepatic pulsations. Laboratory test results were notable for thyroid-stimulating hormone (TSH) completely suppressed at <0.1 mIU/L (normal 0.5 to 5 mIU/L), free thyroxine (T4) 4.2 ng/dL (0.9 to 1.7 ng/dL), thyroid-stimulating immunoglobulin 5.2 (≤1.3), thyrotropin receptor antibody >40 IU/L (0 to 1.75 IU/L), creatinine 3.46 mg/dL (0.59 to 1.04 mg/dL), blood urea nitrogen 71 mg/dL (7 to 20 mg/dL), alanine aminotransferase 126 U/L (7 to 45 U/L), aspartate aminotransferase 128 U/L (8 to 43 U/L), alkaline phosphatase 190 U/L (35 to 104 U/L), total bilirubin 2.7 mg/dL (≤1.2 mg/dL), and direct bilirubin 1.6 mg/dL (≤0.3 mg/dL).

1. Based on the history and physical examination findings, which one of the following diagnoses most likely accounts for the patient’s presentation?

   a. Mitral stenosis leading to heart failure and ascites
   b. Atrial fibrillation leading to tricuspid regurgitation, right heart failure, and ascites
   c. Atrial fibrillation leading to acute renal artery thrombosis
   d. Hypertensive cardiomyopathy leading to left heart failure
   e. Hypertension leading to hypertensive nephropathy

The history and clinical findings of palpitations, tachycardia, and an irregularly irregular rhythm are concerning for atrial fibrillation. The history and clinical findings of personal and family history of thyroid disease, enlarged thyroid, exophthalmos, tremors, brisk reflexes, and hyperdynamic circulation are
consistent with hyperthyroidism as the likely precipitant of her atrial fibrillation. In addition, a 3/6 systolic flow murmur is appreciable over the precordium, which would be consistent with a high-output state in the setting of thyroid storm and with tricuspid regurgitation. Jugular venous distension with prominent CV wave, hepatic pulsations, and positive fluid wave may also be seen with tricuspid regurgitation and right heart failure leading to ascites. However, atrial fibrillation can cause annular dilatation of both the mitral and tricuspid valves, but annular dilatation and valvular regurgitation are significantly greater in the tricuspid valve area. More common causes of primary tricuspid regurgitation include tricuspid valve prolapse, carcinoid syndrome, chest wall trauma, and tricuspid valve endocarditis, but hyperthyroidism is indeed a cause of isolated tricuspid regurgitation and right-sided heart failure. One possible mechanism involves tachycardia and increased right ventricular (RV) preload; high cardiac output and rapid venous return can lead to dilatation of the thin-walled RV, resulting in dilatation of the tricuspid annulus and functional tricuspid regurgitation. Whether the right heart failure is secondary to the severe tricuspid regurgitation or the reverse remains unclear. Although atrial fibrillation can lead to formation of thrombi with embolization to distant sites including the renal artery, these are more often seen in patients who are older and present with hematuria and flank pain, without abdominal distention or ascites. Hypertensive cardiomyopathy and left heart failure alone would not explain her irregular heart rate and rhythm or the progressive abdominal distension with ascites and abdominal pain and neither would hypertensive nephropathy (although, also of note, her vital signs did not indicate hypertension).

An electrocardiogram (ECG) showed atrial fibrillation with rapid ventricular response (RVR) at a rate of 143 bpm without ST-T segment changes suggestive of ischemia. Chest radiography showed clear lung fields and enlarged cardiac silhouette. Cross-sectional computed tomography initially obtained at an outside emergency department before the patient was transferred to Mayo Clinic, showed dilatation of the inferior vena cava and hepatic veins, hepatomegaly, and ascites. Infectious etiologies for liver inflammation were ruled out with extensive testing, but her pain and abnormal liver function tests persisted; thus, core-needle liver biopsy was pursued at the outside hospital as well and was notable for sinusoidal dilation and congestion without fibrosis, concerning for hepatic congestion. Patient was transferred and directly admitted to Mayo Clinic’s gastrointestinal hospital service for further evaluation, and she continued to complain of diffuse abdominal pain.

2. What is the next most appropriate test for evaluation of her clinical presentation?
   a. Transthoracic echocardiography
   b. Transesophageal echocardiography
   c. Cardiac catheterization
   d. Renal ultrasound
   e. Abdominal paracentesis

Although transthoracic echocardiography (TTE) would certainly be indicated to assess for tricuspid regurgitation and right heart failure, suggested by the clinical examination, the patient’s acute abdominal pain in the setting of new ascites must be addressed first. Transesophageal echocardiography to rule out left atrial clot burden would be indicated if electrical external cardioversion was being considered for treatment of the patient’s atrial fibrillation. However, in hyperthyroidism-induced atrial fibrillation, the underlying cause of thyroid dysfunction should be treated first before proceeding to higher-risk interventions such as cardioversion. Likewise, cardiac catheterization to assess for pulmonary hypertension resulting from her heart failure can be deferred until the patient is stable and, furthermore, until the patient’s underlying thyroid condition is treated, as this would likely result in improvement in her cardiopulmonary status. Renal ultrasound would be reasonable to assess the patient’s elevated creatinine, but acute decompensated heart failure can often lead to congestive nephropathy, resulting in elevated creatinine, and, in this patient with ascites and severe abdominal pain, it is critical to first assess
for spontaneous bacterial peritonitis (SBP), which is done via abdominal paracentesis. Although the patient did not have the classical strongest risk factor for developing SBP (liver cirrhosis), she did have other risk factors for developing SBP such as serum total bilirubin >2.5 mg/dL and plasma creatinine ≥1.2 mg/dL with blood urea nitrogen ≥25 mg/dL. Diagnostic abdominal paracentesis revealed peritoneal fluid that was serous appearing and notable for 2778 nucleated cells/mcL with 88% neutrophils, with serum ascites-albumin gradient (SAAG) 1.3 g/dL, and total ascitic protein 3.7 g/dL. Serum total protein was 7.6 g/dL.

3. Which one of the following diagnoses is most consistent with the patient’s ascitic fluid pattern?
   a. Nephrotic syndrome
   b. Malignancy
   c. Pancreatitis
   d. Right heart failure
   e. Liver cirrhosis

Ascites, in the setting of nephrotic syndrome, malignancy, or pancreatitis, would have a SAAG of less than 1.1 g/dL, as they result in a decreased intravascular osmotic gradient, leading to secondary influx of water from the intravascular space to the peritoneal cavity. By contrast, heart failure and liver cirrhosis result in increased pressure in the portal vein, leading to increased hydrostatic pressure in the hepatic vessels, thus favoring fluid shifts from the intravascular space into the peritoneal cavity. Right heart failure is consistent with the patient’s clinical picture and with ascitic values of SAAG >1.1 g/dL and total ascitic protein >2.5 g/dL. As liver cirrhosis interferes with the production of albumin and globulin proteins, total ascitic protein would be less than 2.5 g/dL in patients with cirrhosis, which was not the case.

The patient’s ascitic fluid absolute polymorphonuclear leukocyte (PMN) count was greater than 250 cells/mm³ and thus concerning for spontaneous bacterial peritonitis. Accordingly, cefotaxime 2 grams intravenously every 8 hours was initiated. She was treated for 5 days, with resolution of her abdominal pain and ascitic fluid cultures with no growth of organisms; thus, antibiotics were discontinued, and repeat paracentesis was deferred. Following optimization of the patient’s gastrointestinal issues, she was transferred to the cardiology service for further management of her heart failure.

4. What is the next most appropriate step for optimizing this patient’s cardiac status?
   a. Propylthiouracil (PTU) alone
   b. Amiodarone
   c. Metoprolol
   d. Direct-current cardioversion
   e. Digoxin

Propylthiouracil alone would not be sufficient to counter the effects of tachycardia induced by a hyperadrenergic state. Amiodarone is useful for the restoration of sinus rhythm. Although it is known to cause multiple side effects with long-term use, including pulmonary toxicity, hepatotoxicity, and thyroid dysfunction, it may be used in the short term for conversion of atrial fibrillation. It is important to note a non-negligible risk of thromboembolism associated with the use of amiodarone upon restoration of sinus rhythm. This is further compounded by the fact that thyrotoxicosis is, in and of itself, associated with a risk of thromboembolism via mechanisms that involve the upregulation of prothrombotic factors. Thus, in patients presenting with thyrotoxic atrial fibrillation, cautious use of amiodarone is advised and was not chosen for this patient. Beta blockers are useful for their ability to blunt the hyperadrenergic response in thyrotoxicosis. Propranolol is most commonly used for this purpose owing to its nonselective properties. Metoprolol is a cardioselective beta blocker, which can also be used particularly in patients with reactive airway disease and would be the best therapy for our patient. Direct-current cardioversion is not advised in the absence of hemodynamic compromise or symptoms refractory to medical management. In addition, screening for underlying left atrial appendage thrombus is indicated.
before electric cardioversion. Furthermore, it is unlikely that sinus rhythm will be maintained in the setting of persisting hyperthyroid state and altered atrial tissue refractoriness.-rate control with digoxin may prove resistant owing to its pharmacodynamic properties including increased renal clearance, a higher volume of distribution, and increased Na/K ATPase activity; as such, its use in these patients requires much higher doses, which carries an increased risk of toxicity. Our patient had been prescribed methimazole previously. This was continued to decrease production of excess thyroid hormones. In addition, our patient initially received 25 mg metoprolol tartrate, resulting in decompensation with symptomatic hypotension, but she tolerated a lower dose (12.5 mg metoprolol tartrate every 12 hours) with adequate rate control (HR 90s to 110s).

5. What is the next most accessible and least invasive modality for RV function assessment?
   a. Electrocardiography
   b. Cardiac magnetic resonance
   c. Multidetector computed tomography (MDCT) of the chest
   d. Transesophageal echocardiography (TEE)
   e. Transthoracic echocardiography (TTE)

The RV is a highly complex structure. Electrocardiography may reveal morphological or voltage changes that are suggestive of RV dysfunction. Unfortunately, the specificity and sensitivity of the ECG for this purpose is low. In addition, ECG has limited ability to characterize the degree of RV dysfunction quantitatively. Cardiac magnetic resonance is the gold standard method for RV assessment. Owing to its high spatial resolution, it provides detailed assessment of RV morphology, ejection fraction, contractile reserve, and tissue characterization. However, it would not be the initial modality of choice because of associated costs as well as patient suitability. Multidetector computed tomography is also useful for RV function assessment; however, it is not considered a first-line modality owing to exposure to ionizing radiation as well as contrast media. Transthoracic echocardiography is a quick, affordable, and noninvasive modality that allows for visual assessment and offers a plethora of information regarding right ventricular function. Using 3-dimensional and strain-imaging function, both qualitative and semiquantitative information can be gleaned from TTE. Fractional area change (FAC), tricuspid lateral annular systolic velocity derived from tissue doppler imaging (S'), tricuspid annular plane systolic excursion (TAPSE), and myocardial performance index (MPI) are recommended echocardiographic parameters for assessment of RV function. Transesophageal echocardiography (TEE) is similar to TTE in terms of RV function evaluation; similar to TTE, the modified TAPSE (m-TAPSE) and RV fractional area change (RV-FAC) are TEE-derived indicators of RV function. However, it is more invasive compared with TTE and does not provide any additional information. Thus, it may be a reasonable choice for intraoperative RV assessment but is not the first-line modality for routine assessment of RV function.

Our patient underwent appropriate imaging with a TTE for assessment of RV function. Transthoracic echocardiography revealed severely enlarged inferior vena cava size with no inspiratory collapse, moderately enlarged right ventricular chamber size with moderately reduced systolic function (TAPSE 14 mm; average peak systolic strain -19; S' 8 cm/s), tricuspid annulus dilatation with moderate-to-severe tricuspid regurgitation, normal left ventricular (LV) chamber size with a calculated ejection fraction of 55%, without regional wall motion abnormalities.

DISCUSSION
Poorly controlled hyperthyroidism can have important deleterious cardiovascular sequelae. A high output cardiac state is a common initial complication, as evidenced by the systolic flow murmur and end-organ hypoperfusion. Our patient’s high output circulatory state, created by a thyrotoxic state and exacerbated by significant anemia with hemoglobin 7 g/dL (12.1 to 15.1 g/dL),
likely accelerated RV dysfunction in this patient. Preferential RV dysfunction in our patient was likely the result of RV stunning in concert with pressure overload caused by pulmonary hypertension in (mPAP 44, RV systolic pressure [RVSP] 69 mm Hg). Population studies cite an 8.3% incidence of atrial fibrillation in patients with new-onset hyperthyroidism. The rate of heart failure increases up to 3-fold in patients with atrial fibrillation with a prevalence ranging from 33% to 56%. Our patient’s untreated hyperthyroidism led to several of these complications including atrial fibrillation, new-onset tricuspid annular dilatation and resulting tricuspid regurgitation, isolated RV dilatation and systolic dysfunction with preserved LV contractile function, congestive hepatopathy, as well as renal dysfunction. Thyroid hormones are known to alter cardiac beta-1 and M2-muscarinic receptors as well as ionic channel activity; they exert a permissive effect on beta 1 receptors and so their role in this context is central. Thus, beta blockers are the mainstay treatment for atrial fibrillation with rapid ventricular response. However, given the unknown chronicity of atrial fibrillation in these patients and potential for underlying tachycardia-induced cardiomyopathy, there is a concern for hemodynamic compromise with beta blockade. Interestingly, it has been speculated that the underlying pathophysiology of atrial fibrillation varies based on thyroid function. In hyperthyroid states, there is decreased atrial refractoriness, an important substrate for sustained atrial fibrillation. The cycle of interdependence increases the propensity of occurrence of heart failure in atrial fibrillation and vice versa. Mechanisms involved in heart failure development in the setting of thyrotoxic atrial fibrillation are many. Loss of stroke volume, valve regurgitation with resultant atrial fibrosis, decreased emptying, and tachycardia-induced cardiomyopathy are some important factors that favor the onset of heart failure and atrial fibrillation. Intriguingly, our patient presented with isolated severe tricuspid regurgitation; several factors can account for this. Atrial fibrillation results in secondary tricuspid regurgitation via annular dilatation. In addition, toxic effects of thyroxine on lowering vascular resistance in the pulmonary circuit, with a resulting increase in blood flow and pulmonary hypertension; chronic pressure overload can induce RV remodeling. Increased cardiac output caused by thyrotoxicity induced high output state also leads to RV failure. Initial management of thyrotoxicosis-induced atrial fibrillation and heart failure can be challenging. In patients presenting acutely, initial measures must be focused on achieving hemodynamic stability. The CAN TREAT HFREF+AF algorithm is a clinical mnemonic that provides a step-wise approach to managing newly diagnosed concomitant heart failure and atrial fibrillation, similar to the approach discussed in this educational case. The mnemonic stands for Cardioversion if compromise; Anticoagulation if no contraindications; Normalize fluid balance; Target initial heart rate <110 bpm; Renin—angiotensin—aldosterone modification; Early consideration of rhythm control; Advanced heart failure therapies; and Treatment of other cardiovascular disease. Potential Competing Interests: The authors report no competing interests.

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REFERENCES

CORRECT ANSWERS: 1. b. 2. e. 3. d. 4. c. 5. e.