Journal of the Endocrine Society, 2021, Vol. 5, No. 1, 1–9
doi:10.1210/jendso/bvaa125
Clinical Research Article

Clinical Research Article

Myxedema Heart and Pseudotamponade

Chelsey Baldwin,[1] Jonathan D. Newman,[2] Franco Vallejo,[1] Valerie Peck,[1] Loren Wissner Greene,[1] and Ira J Goldberg[1]

[1]Divisions of Endocrinology, Diabetes, and Metabolism, New York University Grossman School of Medicine, New York, NY, US, and [2]Divisions of Cardiology, New York University Grossman School of Medicine, New York, NY, US

ORCiD number: 0000-0001-5529-2424 (C. Baldwin).

Received: 13 May 2020; Editorial Decision: 16 August 2020; First Published Online: 27 August 2020; Corrected and Typeset: 15 December 2020.

Abstract

Context. Thyroid hormone plays a critical role in cardiovascular function. Severe hypothyroidism can be associated with "myxedema heart" characterized by relative bradycardia and pericardial effusion. Effusions associated with severe hypothyroidism can be large. Despite the large volume of effusions, tamponade is not a common consequence. However, with the incorporation of echocardiography into routine practice for evaluation of effusion, echocardiographic findings suggestive of clinical tamponade occur frequently.

Case Description. We report a series of 3 patients with large pericardial effusions secondary to severe hypothyroidism. These cases serve to demonstrate the discordance between echocardiographic signs consistent with tamponade with a patient's stable clinical hemodynamics. We also report the development of bronchial obstruction, a rare complication of a large effusion due to severe hypothyroidism.

Conclusions. While pericardial effusion associated with severe hypothyroidism has been described for decades, the echocardiographic findings may be less well known and may lead to unnecessary downstream testing or invasive management. We use our case series to facilitate a summary of what is known about the epidemiology, mechanism and physiology, and expected outcomes of myxedema associated pericardial effusion. Finally, in the setting of current paucity of clinical guidelines, we aim to familiarize clinicians with the phenomenon of pseudotamponade and suggest management strategies for myxedema associated pericardial effusion to guide clinicians to use conservative medical management in majority of cases.

Key Words: pericardial effusion, hypothyroidism, Hashimoto's Disease, bradycardia

The relationship between thyroid hormone and cardiovascular function has been well described [1,2]. Thyroid hormone, in the form of triiodothyronine (T3), exerts its action on the myocardium via the nuclear thyroid hormone receptor α. T3 directs inotropic and chronotropic effects on the heart by modulating the expression of sarcoplasmic

ISSN 2472-1972

reticulum calcium channels, β_1 adrenergic receptors, and nuclear thyroid hormone receptor α. Thyroid hormone also indirectly affects cardiac function due to its actions on the vasculature. T3 promotes smooth muscle relaxation and normal arteriolar remodeling [2]. Given the critical role of thyroid hormone in cardiac homeostasis, it is not surprising for the hypothyroid state to cause cardiac dysfunction. Hypothyroidism has been associated with heart failure, cardiomyopathy [1], arrhythmias, systemic diastolic hypertension [3], dyslipidemia, and atherosclerotic disease. Hypothyroidism has also been implicated as a primary etiology of pericarditis, pericardial effusion, and, even more rarely, cardiac tamponade [4,5].

The "myxedema heart" was first described by Zondek in 1918 as a syndrome of cardiac alterations, including large cardiac silhouette, electrocardiogram (ECG) changes indicative of a large pericardial effusion including bradycardia, low voltage, nonspecific T-wave abnormalities, and electrical alternans, which reversed with thyroid hormone extract [6]. Enlarged cardiac silhouette is a common finding in severe hypothyroidism secondary to moderate to large pericardial effusions. The incidence of pericardial effusion in hypothyroidism is 3% in the early mild stage and up to 80% in patients with myxedema [7,8]. Some series report 2% to 10% of moderate to large pericardial effusions are due to hypothyroidism [9-11]. The pathophysiology of pericardial effusions in hypothyroidism is not completely understood. In 1979, Parving et al demonstrated abnormal albumin metabolism in myxedematous patients with a high rate of transcapillary escape and prolonged transit in extravascular space compared to the euthyroid patient, leading to generalized edema [12]. Others have suggested that the serous pericardial effusion in myxedema is due to accumulation of albumin and other plasma proteins due to extravascular escape and impairment of the lymphatic drainage. These processes increase osmotic pressure in the setting of relatively low oncotic pressure gradient between the pericardium and myocardium [7, 12]. Pathophysiologic changes seen with albumin metabolism, protein leak, and impaired lymphatic drainage are all corrected with thyroxine replacement [12].

Despite the fact that myxedema-associated effusion can be large, defined as >500 mL or echo-free space greater than 20mm at its greatest width, the distensibility of the pericardium and slow rate of fluid accumulation protects against hemodynamic compromise due to cardiac tamponade [13,14].

Clinical manifestations of cardiac tamponade include impaired cardiac filling due to increased pressure within the pericardial space, impairing venous return, and systemic perfusion, eventually leading to systemic hypotension and cardiogenic shock. The diagnosis of cardiac tamponade is a clinical diagnosis made in the setting of pericardial effusion associated with tachycardia, hypotension, jugular venous distention, and frequently pulsus paradoxus, defined as inspiratory systolic fall in arterial pressure of ≥10 mmHg. Collateral data supporting the diagnosis of large pericardial effusion include a large cardiac silhouette on chest radiograph and electrical alternans on ECG. However, the latter clinical findings may lack both sensitivity and specificity [15], especially early in the disease course.

Traditionally, cardiac tamponade due to myxedema associated pericardial effusion was considered to be a rare complication due to the slow accumulation of fluid in the pericardial space [4,5]. The first case of cardiac tamponade due to myxedema was described by Martin and Spathis in 1965 [5]. However, in more recent patient series the frequency of echocardiographic signs of tamponade was reported to be as high as 50% in patients with severe hypothyroidism [4]. We will present a series of 3 patients with large pericardial effusions associated with severe hypothyroidism who demonstrated echocardiographic findings consistent with tamponade, but without hemodynamic compromise (Table 1). We will use these cases to explore the echocardiographic findings in severe hypothyroidism. We then review the literature on myxedema pericardial effusions to give guidance to clinicians on the management of this condition.

Case Presentations

Case 1

A 63-year-old woman with past medical history of tobacco abuse and hypertension, who was on no home medications and had no medical care for the last 14 years, presented after a mechanical fall. Prior to her fall, her family reported a decline in functional status over 3 months.

Vital signs were 95.8°F, 149/85 mmHg, heart rate (HR) 56 beats per minute (bpm), 97% oxygen saturation on room air. On exam, she exhibited right-sided facial droop, flaccid right upper and lower extremities, and trace bilateral pitting edema overlying bilateral shins. Cardiac rhythm was regular. Thyroid, pulmonary, and abdominal exams were without pertinent positive findings.

Laboratory was remarkable for thyroid-stimulating hormone (TSH) 42 uIU/mL (0.35-4.8), free thyroxine (fT4) 0.28 ng/dL (0.9-1.9), thyroid peroxidase antibody (TPO) 201 IU/mL (0.0-34.9), early morning cortisol 12.8 ug/dL [6-21], brain natriuretic peptide 725.6 pg/mL (0-100), creatine kinase 1766 U/L (96-140), and troponin 1.9 ng/mL (<0.06).

The patient was admitted to the neurology service for acute basal ganglion ischemia demonstrated on computed tomography. Laboratory testing suggested rhabdomyolysis and hypothyroidism. ECG demonstrated

Table 1. Summary of cases

	Case 1	Case 2	Case 3
Last contact with healthcare prior to presentation	14 years	1 year	Unknown
Presentation	Generalized weakness and lethargy	Generalized weakness and mechanical fail	Severe lethargy and mild dyspnea
Vital signs	BP: 149/85 HR:56 RR:10 T: 95.8° O_2 sat; 97% on room air	BP: 150/113 HR: 83 RR: 14 T: 98° O_2 sat: 100% on room air	BP: 162/90 HR: 89 RR: 16 T: 97.3° O_2 sat: 97% on 2L 02
Pulsus paradoxus	No	No	No
Thyroid function tests	TSH: 42.4 fT4: 0.28	TSH: 198.7 fT4: <0.02	TSH: 87 fT4: 0.35
TPO antibody (0.0-34.9 IU/mL)	201	20.2	3305
TTE findings	• RV and RA collapse during diastole • RA pressure: >15 mmHg • Respiratory variation of the mitral inflow • IVC plethora: no comments	• RV and RA collapse during diastole • RA pressure: >15 mmHg • Flow variation: no comments • Dilated IVC	• RV and RA collapse during diastole • RA pressure approximately 15 mmHg. • Significant variation of flow velocity across the mitral valve • Dilated IVC
Pericardial fluid analysis	n/a	• Yellow straw colored –50 RBC, 23 WBC, 77% neutrophils • LDH 391, protein 5.6, glucose 83 • Neg culture, gram stain, AFB and cytology	• Serosanguinous fluid –4100 RBC, 102 WBC. 3% neutrophils, 80% lymphocytes • Neg culture, gram stain, AFB and cytology
Initial treatment	Levothyroxine 50 mcg/d IV	Levothyroxine 25 mcg/d IV	Levothyroxine 200 mcg/d IV once, then 75 mcg/d IV

Abbreviations: AFB, acid fast bacilli; BP, blood pressure; fT4, free thyroxine; HR, heart rate; IV, intravenous; IVC, inferior vena cava; LDH, lactate dehydrogenase O_2 sat, oxygen saturation; RA, right atrial; RBC, red blood cells; RR, respiratory rate; RV, right ventricle; T, temperature; TTE, transthoracic echocardiogram; TPO, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; WBC, white blood cells.

sinus bradycardia with T-wave flattening (Fig. 1A). A transthoracic echocardiogram, obtained for work-up of ischemic stroke, showed concentric ventricular hypertrophy, a large pericardial effusion with echocardiographic signs of tamponade including elevated right atrial (RA) pressure, right ventricle (RV) diastolic collapse, and significant respiratory variation in diastolic left ventricular filling. The patient did not demonstrate pulsus paradoxus on clinical exam. Given the patient's stable hemodynamic state pericardiocentesis was deferred and she was treated with 50 mcg of intravenous (IV) levothyroxine; the IV formulation was selected due to dysphagia. Repeat echocardiogram 8 weeks after the initial study demonstrated a significant reduction in the size of pericardial effusion with normalized diastolic filling of all cardiac chambers. The patient was discharged on 150 mcg (2.3mcg/kg) of levothyroxine daily.

Case 2

A 61-year-old female with a past medical history of rheumatoid arthritis, polymyositis, interstitial lung disease, and hypothyroidism presented with 3 days of generalized weakness. Over the last several years, the patient had noted dry skin, cold intolerance, and a change in voice quality. She had not seen a physician or taken medications for approximately 1 year.

Vital signs 98.0°F, 150/113 mmHg, HR 83 bpm, and 100% oxygen saturation on room air. She was a chronically ill appearing, cachectic (body mass index 18), but oriented. She had slurred speech, jugular venous distention to the level of the mandible, muffled cardiac sounds, and rales at the base of the right lung but no wheezes. In addition, she had symmetric upper (4/5) and lower (3/5) limb weakness, bilateral no pitting edema overlying the tibia up to her knees, diffusely dry skin with scale on limbs, and

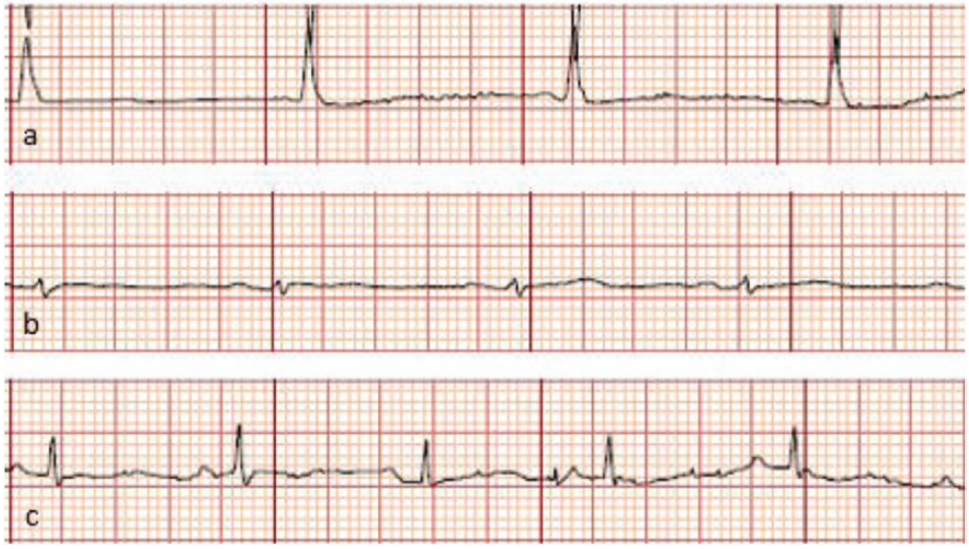

Figure 1. Lead II ECG findings on admission demonstrating findings consistent with myxedema heart. 1a (Case 1) demonstrates sinus bradycardia with flattened t waves; 1b (Case 2) and 1c (Case 3) with low voltage and T-wave flattening.

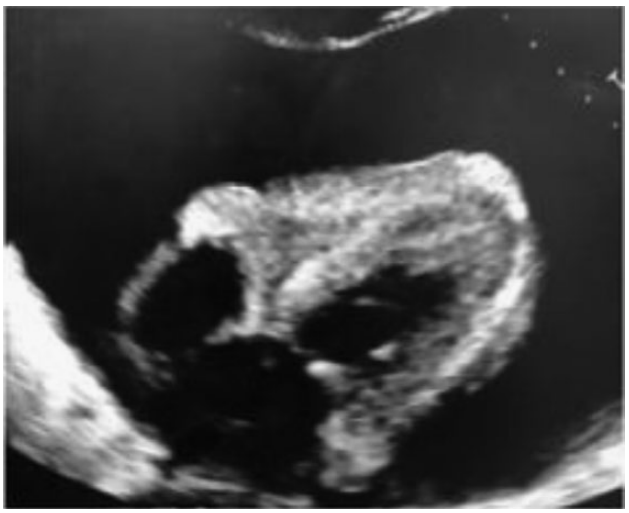

Figure 2. Case 3 transthoracic echocardiogram, subxiphoid view, demonstrating large pericardial effusion with RV collapse during diastole.

delayed relaxation of deep tendon reflexes. Thyroid exam was normal.

Laboratory evaluation was notable for TSH 198.7 uIU/mL (0.35-4.8), fT4 < 0.10ng/dL (0.9-1.9), TPO 20.2 IU/mL (0.0-34.9), random cortisol 8.2 ug/dL [6-21], and sodium 140 mmol/L (137-147).

Her ECG was notable for low voltage, and T-wave flattening (Fig. 1B). TTE showed a large pericardial effusion with pericardial thickening and plethora of the inferior vena cava (IVC) indicating right atrial pressure elevation, along with diastolic collapse of the RA and RV. This patient also did not have pulsus paradoxus on exam.

The patient was admitted to the cardiac intensive care unit (ICU) where she underwent pericardiocentesis with placement of pericardial drain for determination of etiology of the pericardial effusion in the setting of her concurrent rheumatologic disease and cachexia, in addition to severe hypothyroidism. The pericardiocentesis removed 1.45 L of straw-yellow pericardial fluid, which contained 50 red blood cells/mm^3 23 white blood cells (WBC)/mm^3 (<499 WBC/mm^3) that were 77% neutrophils (<24%), 12% lymphocytes, and 7% monocytes. Microbiologic studies including mycobacterium fluid cultures were negative for infection, and fluid cytology for malignancy were negative. Thus, the etiology of effusion was felt to be hypothyroidism.

The patient was treated with intravenous levothyroxine, initial dose of 25 mcg IV daily. The pericardial drain continued to drain 100 to 200 mL daily. On hospital day 20 the patient developed a low-grade fever and her pericardial drainage grew *Proteus* and *Enterococcus*. She was then treated with ampicillin 3 g—sulbactam every 6 h for 7days then transitioned to amoxicillin 875 mg—clavulanate 125 mg every 12 h to complete a 14-day treatment. The patient's generalized weakness improved, and she transitioned to oral levothyroxine 125mcg (2.8 mcg/kg) prior to discharge.

Case 3

A 66-year-old Bangladeshi female with a medical history of hypothyroidism presented with cough, lethargy, and dyspnea. The patient's husband reported the wife's facial

swelling and dry skin over the last several months and a decline in her independent function over the several preceding weeks. Two weeks prior to presentation she began to experience dyspnea, which became progressively severe associated with cough productive of white, frothy sputum unresponsive to antibiotics. He also reported she was noncompliant with her home medications of levothyroxine and omeprazole.

On presentation, vital signs were 97.3°F, 162/90 mmHg, HR 89 bpm, 97% oxygen saturation on 2 L O_2 via nasal cannula. On examination, the patient was lethargic but oriented. She had swollen facial features, most prominent at the circumference of ocular orbits, distant cardiac sounds, diffuse expiratory wheeze without rales, diffusely dry skin, delayed relaxation of deep tendon reflexes, and no thyromegaly.

Chest X-ray demonstrated enlargement of the cardiac silhouette and congestion of the pulmonary vessels. ECG demonstrated T-wave flattening (Fig. 1C). Transthoracic echocardiogram was notable for a large pericardial effusion with features concerning for tamponade (Fig. 2). Findings included IVC plethora, RA/RV diastolic collapse, and significant respiratory variation in diastolic left ventricular filling across the mitral valve. Recurrent measurements for pulsus paradoxus were normal.

Laboratory exam included TSH 87.47 ulU/mL (0.35-4.8), fT4 0.35 ng/dL (0.9-1.9), free triiodothyronine 1.2 pg/mL (2.3-4.2), TPO 3305 lU/mL (0.0-34.9), morning cortisol 12.0 ug/dL (6-21), sodium 136 mmol/L (137-147). Arterial blood gas was pH 7.3 (7.35-7.45), partial pressure of carbon dioxide 75.4 mmHg (35-45), O_2 94.5 mmHg (80-100) on 2 L of nasal oxygen.

The patient was admitted to medical ICU for acute hypoxic hypercapnic respiratory failure requiring continuous positive airway pressure. She was treated for severe hypothyroidism with intravenous levothyroxine, initial bolus of 200 mcg, followed by 75 mcg daily. Her alertness rapidly improved, however, her respiratory status failed to recover. A contrast computed tomography chest showed compression of the left main stem bronchus and resultant atelectasis due to the large pericardial effusion (Fig. 3). Pericardial drainage was performed and 1.1 L of serosanguinous fluid was removed, followed by marked improvement in her respiratory status over the 24 h following her procedure. She was weaned off supplemental oxygen within 72 h postprocedure. The pericardial fluid had 4100 red blood cells/mm^3, 102 WBC/mm^3 (<499 WBC/mm^3), 3% neutrophils (<24%), 80% lymphocytes, and 1% monocytes. Microbiology cultures and cytology were negative. She was discharged on oral levothyroxine 112 mcg (1.5 mcg/kg) daily.

Discussion

We present 3 cases of myxedema pericardial effusion that highlight the hemodynamic stability of hypothyroid patients with large pericardial effusions with significant echocardiographic findings. All 3 patients had biochemical and clinical evidence of severe hypothyroidism. Our first case demonstrates that patients with large pericardial effusions due to hypothyroidism can be managed conservatively with thyroid hormone replacement despite echocardiographic findings of chamber compromise and abnormal diastology. Our second case supports the use of pericardiocentesis when the underlying etiology for the effusion cannot be reasonably limited to hypothyroidism. It should be noted, however, that prolonged pericardial drainage may increase the risk of nosocomial infections. Our final case exhibits a rare complication—to our knowledge ,the first reported case—of a large effusion due to hypothyroidism causing compression of the left mainstem bronchus. The patient presented with airway obstruction, and only after cross sectional imaging was it apparent that the large pericardial effusion caused bronchial compression. A single therapeutic pericardiocentesis and concomitant thyroid replacement was sufficient for symptomatic relief. This case demonstrates the need for therapeutic evacuation of a large effusion due to hypothyroidism when there are extenuating circumstances.

Patients with pericardial effusions due to hypothyroidism typically present with complains of dyspnea (61.1%) [4], cough (25%) [4], and/or chest pain (13.9%) [4] in the setting of clinical and biochemical features of severe hypothyroidism including lethargy, facial swelling, dry skin with nonpitting edema, delayed relaxation of deep tendon reflexes, low thyroxine levels, and abnormal TSH

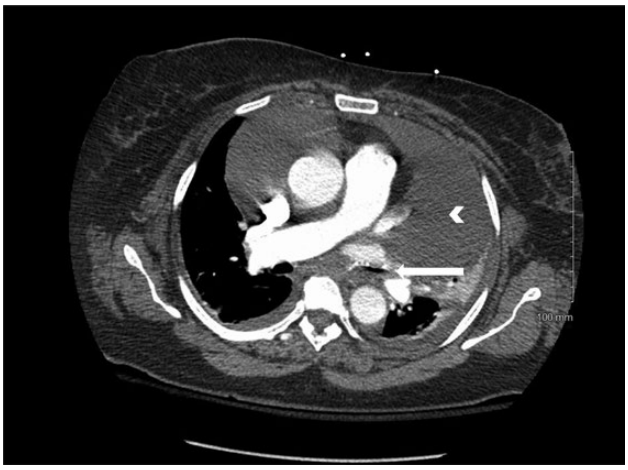

Figure 3. Case 3 axial computed tomographam demonstrating large pericardial effusion (arrowhead) causing narrowing of distal left mainstem bronchus.

levels (elevated in primary hypothyroidism and low or inappropriately normal in secondary or tertiary hypothyroidism). Elevation of TSH greater than 30 mU/L was seen in all 3 of our cases and 95% in other series [4]. The most common causes of severe hypothyroidism in our case series was medication noncompliance or undiagnosed hypothyroidism in patients with prolonged absence from medical attention.

Initial evaluation of patients presenting with dyspnea, a common symptom of severe hypothyroidism with pericardial effusion, typically includes a chest X-ray and ECG. Each of our patients had an enlarged cardiac silhouette. Concurrent pulmonary effusion due to serositis may be seen. Consolidations of the pulmonary parenchyma would be unexpected without a concurrent disease process. ECG changes associated with severe hypothyroidism include low voltage, sinus bradycardia, flattened T, or inverted T waves, prolonged QTc predisposing patient to risk of development of torsade de pointes ventricular tachycardia, and, rarely, AV block [4,16]. Of note, only 1 of our patients was bradycardic, and none were tachycardic as might be expected with large pericardial effusions limiting chamber filling. The abnormalities of the chest X ray and ECG require evaluation for pericardial effusion by echocardiogram based on current guidelines [17].

Pericardial effusions associated with severe hypothyroidism is not an uncommon finding [9-11]; however, it is rarely associated with clinical signs of tamponade. The frequency of tamponade physiology associated with myxedema pericardial effusions is greatly impacted by how the clinician defines tamponade. The diagnosis of cardiac tamponade is a clinical diagnosis made in the setting of hypotension, jugular distention, and tachycardia, often with pulsus paradoxus. None of our patients fit these clinical criteria.

We describe echocardiographic features of large pericardial effusions in the setting of severe hypothyroidism without tamponade physiology. Evaluation of effusion with echocardiography is recommended by European Society of Cardiology [17]. Findings associated with tamponade include IVC plethora due to increased right atrial pressure, RA and RV diastolic collapse, and respiratory variation of diastolic flow across the mitral value. However, these findings lack specificity and sensitivity. Right ventricular diastolic collapse can be seen with hypovolemic states and large pleural effusions, and right ventricular diastolic collapse may be absent in tamponade in patients with high pulmonary pressures. Respiratory variation of mitral valve inflow may occur in obstructive pulmonary disease, pulmonary embolism, and right ventricular infarction [15]. In 2010, Wang et al reported that 50% of their patients with pericardial effusion associated with hypothyroidism had echocardiographic evidence of cardiac tamponade [4]. However, only 22% of patients in the 2010 Wang et al study meet the traditional clinical definition of tamponade of exhibiting pulsus paradoxus or unstable hemodynamics. All of our patients demonstrated echocardiographic signs of tamponade, but none had clinical evidence of tamponade physiology. Two of our patients underwent pericardiocentesis for diagnosis or management of noncardiac complications, and the third was successfully treated without invasive interventions.

Slow accumulation of fluid in the pericardial space allows for a rightward shift of the pressure-volume curve allowing for large volumes of fluid to collect prior to reaching limit of pericardial stretch, at which point a steep rise in pericardial pressure results in cardiac chamber collapse [15,18]. While larger volumes of fluid can be compensated for longer in disease processes with slow accumulation (ie, myxedema associated effusion), the pressure-volume curve will at some volume exhibit a steep rise in pressure leading to tamponade physiology. However, myxedema-associated pericardial effusion appears to have a prolonged period of time when echocardiographic evidence of tamponade may be present without clinical features of tamponade, as exemplified by our case series, and can be reversed with thyroid hormone replacement alone, as demonstrated in Case 1. We hypothesize accumulation of large volume effusion results in a rise in oncotic pressure within the pericardial space, which balances with osmotic pressure developed by capillary protein leak, protecting these patients from accumulation of fluid beyond the maximal stretch of the pericardium at which point cardiovascular compromise is expected (Fig. 4).

There are no available specific clinical guidelines to direct the evaluation and treatment of myxedema associated pericardial effusion. We suggest once the diagnosis of hypothyroidism is determined to be the most likely etiology of pericardial effusion, hemodynamic stability should be carefully confirmed by physical exam, including use of maneuvers to elicit pulses paradoxus, if present. Echocardiography may demonstrate echocardiographic features with large pericardial effusions not associated with hemodynamic instability that resolve with thyroid hormone replacement alone, leading us to suggest these findings are consistent with "pseudotamponade."

Thyroid hormone replacement, in the form of levothyroxine, reverses the progression of fluid accumulation and prevents cardiac collapse. Pericardial effusions due to severe hypothyroidism will begin to resolve even prior to biochemical and clinical euthyroidism. Complete resolution of the effusion occurs within 8 to 26 weeks [4,19] without invasive management. The American Thyroid Association (ATA) recommends that the initial

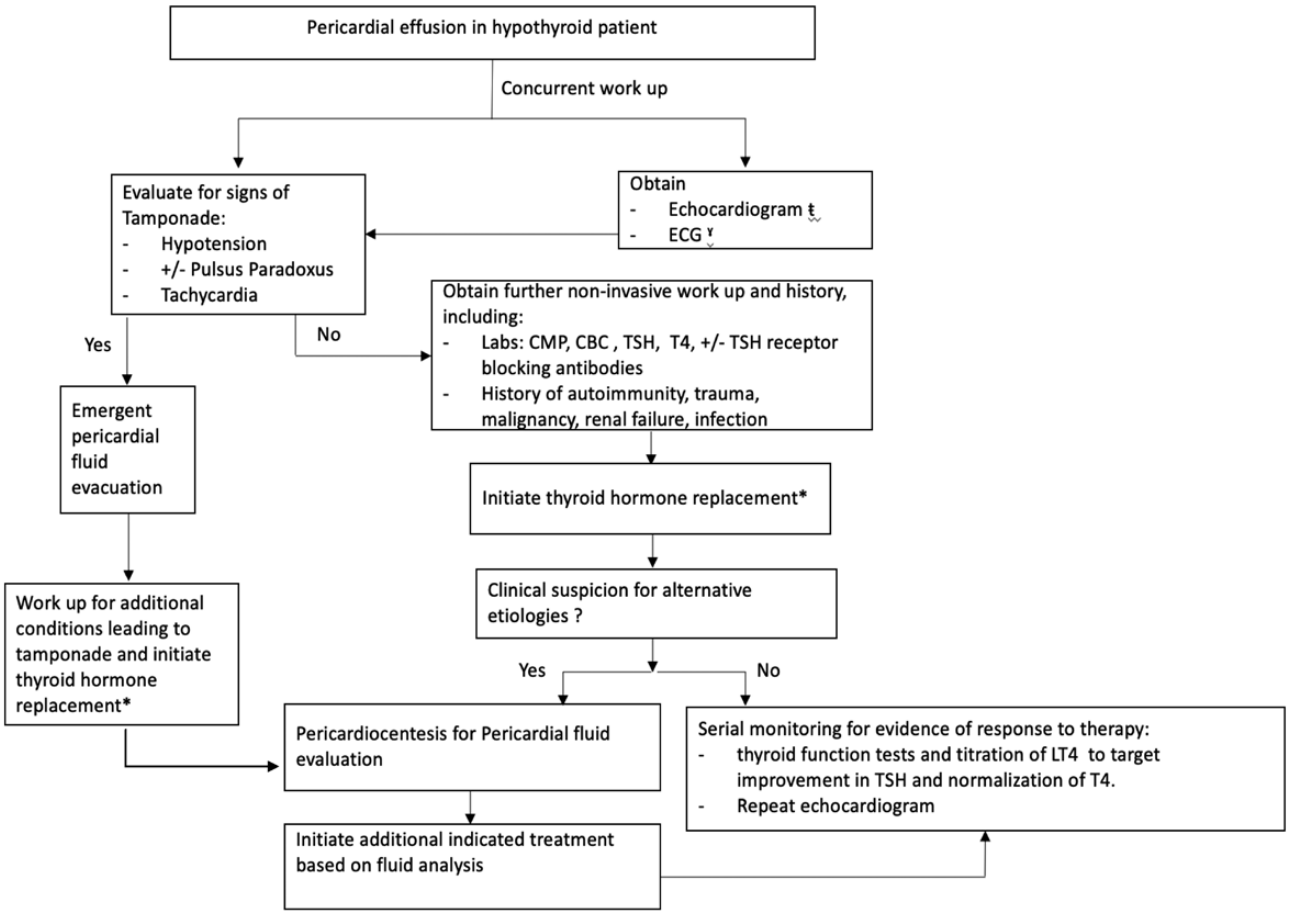

Figure 4. Pericardial effusion management in a hypothyroid patient. ŧ Echocardiographic findings of IVC plethora due to increased right atrial pressure and RA and RV diastolic collapse; respiratory variation of diastolic flow across the mitral valve may be present in the absence of hemodynamic compromise consistent with pseudotamponade. ¥ Findings on ECG consistent with myxedema heart include low voltage, flattened or inverted T waves, relative bradycardia, prolongation of QTc, and ±electrical alternans. *Initial dose of levothyroxine dependent on clinical severity of hypothyroidism and history/suspicion of cardiac comorbidities.

levothyroxine doses be given intravenously until the patient demonstrates clinical improvement [20]. Even very low doses of levothyroxine can correct capillary permeability [19]; therefore, initial doses can be more conservative than estimates for full replacement by body weight (1.6 µg/kg/day) as suggested by ATA for patients with myxedema coma. Often clinicians reduce the dose by 25% when dosing intravenously due to improved bioavailability; further dose reductions should be considered in patients with history of or suspected history of untreated coronary artery disease [20,21]. An initial bolus of levothyroxine should be reserved for the most severe presentations of hypothyroidism. In Case 3, a bolus of 200 mcg of IV levothyroxine was given as this patient necessitated ICU admission for altered mental status and hypercapnic respiratory failure in setting of low normal body temperature, concerning for myxedema coma. Therefore, we felt early aggressive intervention was indicated based on our clinical suspicion, despite known cardiac risks of tachycardia, arrhythmia, and myocardial infarction [20]. Also, the doses of levothyroxine at discharge were higher than ATA prediction for full replacement in Case 1 and Case 2, with discharge doses of levothyroxine of 2.3 mcg/kg and 2.8 mcg/kg, respectively. Our doses were guided by serial laboratory tests to demonstrate normalization of fT4 and trend of TSH improvement. Levothyroxine resistance demonstrated in these patients can be due to concurrent medication use altering gastric pH or levothyroxine absorption, alterations of gut flora, concurrent autoimmune disease affecting the gut, and noncompliance with fasting after administration of levothyroxine tablet [22]. In Case 1, the patient was started on proton pump inhibitor for gastric protection in the setting of dual antiplatelet therapy use for stroke, which made have led to poor dissolution and therefore bioavailability of levothyroxine tablet. In Case 2, the patient's phenotype of polyautoimmunity could be consistent with concurrent gastrointestinal conditions impairing levothyroxine absorption. Autoimmune atrophic gastritis and celiac disease have been associated with concurrent thyroid autoimmunity [23,24] and may provide an explanation for the

requirement of higher doses of levothyroxine. Additionally, this patient required antibiotics that may have altered gut flora resulting in impaired levothyroxine absorption [22]. Given the possibility of changes to medication regimen and gut flora post discharge, follow-up is imperative to avoid over treatment and work-up concomitant conditions.

In addition to levothyroxine, clinicians should consider a stress dose of glucocorticoid prior to levothyroxine if unable to rule out concurrent adrenal insufficiency [20]. The use of concurrent intravenous liothyronine is reserved for patients with myxedema coma and those without clinical improvement with levothyroxine monotherapy.

In some cases, the etiology of pericardial effusion is unclear. While laboratory testing consistent with severe hypothyroidism in the absence of typical beta-adrenergic driven tachycardia (HR less than 90 bpm) is highly suggestive of hypothyroidism as the underlying cause of the pericardial effusion, it may be necessary to rule out concurrent disease processes. In Case 2, known rheumatologic disease raised the concern for possible alternative explanation of effusion. Similar diagnostic confusion may be present in patients with concurrent trauma, sepsis, renal failure, or malignancy. The majority of patients who develop clinical cardiac compromise in the form of tamponade due to myxedema associated pericardial effusion will have precipitating factor-like infection or trauma [4]. Therefore, a diagnostic pericardiocentesis may be helpful when there is diagnostic uncertainty. European Society of Cardiology guidelines for diagnosis and management of pericardial disease suggest that if a specific etiology of pericarditis and effusion is suspected or high risk features (such as fever, subacute onset, large pericardial effusion, cardiac tamponade, or lack of response to one week of anti-inflammatory therapy) are present, diagnostic pericardiocentesis is indicated. Pericardiocentesis or surgical intervention is also required when the clinical diagnosis of tamponade is made, again reflecting the importance of the defining tamponade clinically to avoid unnecessary intervention.

A volume of 50 to 100 mL of pericardial fluid is satisfactory for diagnostic testing. Also, aspiration of relatively small volume may result in a decline in pericardial pressure in patients with tamponade physiology [15].

There are no specific clinical guidelines to direct the evaluation and treatment of myxedema associated pericardial effusion. We extrapolate from the 2015 European Society of Cardiology guidelines for evaluation and management of pericardial disease and the 2014 ATA guidelines for hypothyroidism, along with experiences reported in the literature supported by our 3 additional cases to suggest a method for the appropriate management of myxedema associated pericardial effusion (Fig. 4). In summary, patients found to have large pericardial effusion and stable hemodynamics investigation for etiology should include TSH and fT4. Laboratory evidence and clinical syndrome consistent with severe hypothyroidism in the context of a large pericardial effusion with relative bradycardia is highly consistent with myxedema associated pericardial effusion. TSH receptor blocking antibodies are used by some clinicians in patients with hypothyroidism as a mechanistic indicator of atrophic hypothyroidism, which may be associated with severe clinical presentations of hypothyroidism [25]. These antibodies were not obtained in our patients due to the clinically apparent severity of their conditions and lack of readily available quick turn-around cell-based bioassays to prove functional inhibition of TSH receptor. Echocardiography is essential for the diagnosis of pericardial effusions; however, it may demonstrate echocardiographic findings associated with tamponade physiology without impending cardiovascular compromise, consistent with "pseudotamponade." Therefore, the diagnosis of tamponade should be reserved for patients demonstrating clinical features of tamponade, pulsus paradoxus, and hemodynamic compromise. Patients with myxedema or severe hypothyroidism may be protected against clinical manifestations of tamponade through the slow accumulation of pericardial fluid. Hypothyroidism associated pericardial effusions rarely accumulate fluid beyond maximal extension of the pericardium, protecting the patient from clinical features of tamponade. Because pericardial effusions of hypothyroidism will resolve with levothyroxine, monotherapy pericardiocentesis should be reserved for cases of diagnostic confusion and rare cases of cardiovascular compromise or compromise of adjacent vital structures. Clinical evidence of tamponade physiology in the setting of myxedema associated pericardial effusion may support investigation for other underlying causes of pericardial effusion.

Acknowledgments

Financial Support: Dr. Goldberg receives salary support from NIH grants HL45095, 73029, 135987 and 92969 and an AHA SFRN in Cardiometabolic Disease.

Additional Information

***Correspondence*:** Chelsey Baldwin, MD, Division of Divisions of Endocrinology, Diabetes, and Metabolism, 435 East 30th Street, Science Building 616, New York, NY 10016. E-mail: Chelsey.Baldwin@nyulangone.org.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

References

1. Grais IM, Sowers JR. Thyroid and the heart. *Am J Med*. 2014;**127**(8):691-698.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;**344**(7):501-509.

3. Klein M, Pascal V, Aubert V, Weryha G, Danchin N, Leclére J. [Heart and thyroid]. *Ann Endocrinol (Paris)*. 1995;**56**(5):473-486.
4. Wang JL, Hsieh MJ, Lee CH, et al. Hypothyroid cardiac tamponade: clinical features, electrocardiography, pericardial fluid and management. *Am J Med Sci*. 2010;**340**(4):276-281.
5. Martin L, Spathis GS. Case of myxoedema with a huge pericardial effusion and cardiac tamponade. *Br Med J*. 1965;**2**(5453):83-85.
6. Zondek H. Das Myxödemherz [The myxedema heart]. *Münch Med Wochenschr*. 1918;**43**:1180-1182.
7. Kabadi UM, Kumar SP. Pericardial effusion in primary hypothyroidism. *Am Heart J*. 1990;**120**(6 Pt 1):1393-1395.
8. Hardisty CA, Naik DR, Munro DS. Pericardial effusion in hypothyroidism. *Clin Endocrinol (Oxf)*. 1980;**13**(4):349-354.
9. Sagristà-Sauleda J, Mercé J, Permanyer-Miralda G, Soler-Soler J. Clinical clues to the causes of large pericardial effusions. *Am J Med*. 2000;**109**(2):95-101.
10. Levy PY, Corey R, Berger P, et al. Etiologic diagnosis of 204 pericardial effusions. *Medicine (Baltimore)*. 2003;**82**(6):385-391.
11. Ma W, Liu J, Zeng Y, et al. Causes of moderate to large pericardial effusion requiring pericardiocentesis in 140 Han Chinese patients. *Herz*. 2012;**37**(2):183-187.
12. Parving HH, Hansen JM, Nielsen SL, Rossing N, Munck O, Lassen NA. Mechanisms of edema formation in myxedema–increased protein extravasation and relatively slow lymphatic drainage. *N Engl J Med*. 1979;**301**(9):460-465.
13. Manolis AS, Varriale P, Ostrowski RM. Hypothyroid cardiac tamponade. *Arch Intern Med*. 1987;**147**(6):1167-1169.
14. Saito Y, Donohue A, Attai S, et al. The syndrome of cardiac tamponade with "small" pericardial effusion. *Echocardiography*. 2008;**25**(3):321-327.
15. Chandraratna PA, Mohar DS, Sidarous PF. Role of echocardiography in the treatment of cardiac tamponade. *Echocardiography*. 2014;**31**(7):899-910.
16. Schoenmakers N, de Graaff WE, Peters RH. Hypothyroidism as the cause of atrioventricular block in an elderly patient. *Neth Heart J*. 2008;**16**(2):57-59.
17. Adler Y, Charron P, Imazio M, et al.; ESC Scientific Document Group. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;**36**(42):2921-2964.
18. Spodick DH. Acute cardiac tamponade. *N Engl J Med*. 2003;**349**(7):684-690.
19. Khaleeli AA, Memon N. Factors affecting resolution of pericardial effusions in primary hypothyroidism: a clinical, biochemical and echocardiographic study. *Postgrad Med J*. 1982;**58**(682):473-476.
20. Jonklaas J, Bianco AC, Bauer AJ, et al.; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;**24**(12):1670-1751.
21. Oe K, Yamagata T, Mori K. Acute myocardial infarction following hormone replacement in hypothyroidism. *Int Heart J*. 2007;**48**(1):107-111.
22. Virili C, Trimboli P, Centanni M. Novel thyroxine formulations: a further step toward precision medicine. *Endocrine*. 2019;**66**(1):87-94.
23. Kahaly GJ, Frommer L, Schuppan D. Celiac disease and glandular autoimmunity. *Nutrients*. 2018;**10**(7):814.
24. Rodriguez-Castro KI, Franceschi M, Miraglia C, et al. Autoimmune diseases in autoimmune atrophic gastritis. *Acta Biomed*. 2018;**89**(8-S):100-103.
25. Diana T, Olivo PD, Kahaly GJ. Thyrotropin receptor blocking antibodies. *Horm Metab Res*. 2018;**50**(12):853-862.