Case Report
Pericardial Tamponade and Elevated Serum CA-125 Level in Inadequately Treated Hypothyroidism


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Cardiac tamponade is a medical emergency and must be managed promptly, and reaching a diagnosis is imperative to prevent recurrence. Herein, we present a case of a young female patient that presented with progressive shortness of breath and abdominal distension and was found to have cardiac tamponade with the finding of elevation of a blood tumor marker, CA-125, in the setting of nonadherence to thyroid replacement therapy. She was managed by surgical pericardial window and abdominal paracentesis, with replacement of thyroid hormones leading to resolution of the tamponade and ascites. CA-125 elevation associated with cardiac tamponade and myxedema ascites due to hypothyroidism is very rare, and we aim to shed light on the importance of having a broad differential when approaching cardiac tamponade and understand the association between CA-125 and hypothyroidism.

1. Introduction
Primary hypothyroidism is prevalent in 4.6% of the US population, with a higher prevalence in women. According to the American Thyroid Association, reportedly one in eight women will develop a thyroid disorder [1]. The disease is usually life-long but can be well controlled with adherence to medical management. However, poor medical care or nonadherence can put the patient at risk for complications, which can range from mild to life-threatening, the latter of which can include the accumulation of fluids in the body cavities presenting as cardiac tamponade and myxedema ascites, which occur in 4% of mild cases, and can go up to 30-80% in severe cases [1, 2]. Cardiac tamponade secondary to hypothyroidism is rare as the fluid accumulates slowly, gradually progressing to pericardial sac distension [2]. Herein, we report a case of a young female patient with uncontrolled postthyroidectomy hypothyroidism in the setting of medication nonadherence who presented with elevated CA-125 levels, cardiac tamponade, and ascites, all of which were secondary to severe hypothyroidism.

1.1. Patient Information. A 31-year-old female with hypothyroidism secondary to total thyroidectomy for papillary thyroid carcinoma, with chronic medication nonadherence, presented with abdominal distension that had been progressing over the 3 months prior to admission. She also complained of worsening dyspnea which progressed to inability to finish her sentence, along with back pain radiating to her shoulder that started one hour prior to admission.

The patient had a history of papillary thyroid carcinoma status postthyroidectomy one year prior to admission, with the patient reporting a several-month history of medication nonadherence. The patient had no personal or family cardiac history.

1.2. Clinical Findings. Upon presentation, her blood pressure was 103/90 mmHg, heart rate ranged from 75 to 89 beats/min, respiration was 16 breaths/min, SpO2 was 98% on room air, and she was afebrile. Cardiovascular examination revealed a jugular venous pressure of 15 cm H2O, distant heart sounds, and no murmurs, and Kussmaul’s sign was not present. However, pulsus paradoxus was not appreciated, and peripheral
edema was absent. There was a well-healed horizontal neck scar from a previous total thyroidectomy, also known as a Kocher incision. She was noted to have mild facial swelling, mild generalized hypopigmentation over her skin, and enlarged nontender abdominal girth.

1.3. Diagnostic Assessment. Laboratory analysis revealed serum TSH level > 100 mIU/L and elevated levels of CA-125 of 230.1 U/mL. A diffuse low voltage electrocardiogram (EKG) (Figure 1) raised a suspicion for pericardial effusion, which was confirmed on initial enhanced computed tomography (CT) of the abdomen and pelvis, showing large pericardial effusion and peritoneal fluid collection (Figure 2). An urgent transthoracic echocardiogram (TTE) confirmed the very large pericardial effusion with a swinging heart, right ventricular collapse, and marked mitral inflow respiratory variation (Figure 3), for which the patient was taken for an emergent pericardial window with removal of 1.5 liters of serous fluid and pericardial drain placement. Pericardial fluid analysis and pericardial tissue demonstrated exudative effusion with reactive mesothelial cells, which were positive for calretinin and negative for tumor marker results such as MOC31, BerEp4, TTF1, and mucin. Pericardial effusion also had negative cultures and cytology.

It was initially difficult to reconcile such a profound presentation of fluid overload with a unifying diagnosis. Pregnancy was first ruled out. Along with hypothyroidism, a highly elevated CA-125 led to considering peritoneal and gynecologic malignancies at the top of the differential diagnosis. Autoimmune (e.g., SLE and rheumatoid arthritis); bacterial, fungal, and viral infections; and postviral complications were considered, along with congenital disorders (e.g., Wilson’s disease).

1.4. Investigations. A follow-up TTE (Figure 4) demonstrated a small pericardial effusion, a thickened and echogenic right ventricular (RV) free wall, and diffuse mild hypokinesis of the left ventricle (LV) with an Ejection Fraction (EF) of 45-

Figure 1: Electrocardiogram at presentation showing a sinus rhythm with a heart rate around 90 bpm and diffuse low voltage in both precordial and limb leads.

Figure 2: CT of the abdomen and pelvis with IV contrast on day 1. Mild bilateral basilar foci of atelectasis. Large pericardial effusion (yellow arrows in (b) and (c)). Large amounts of ascitic fluid (red arrows in (a)–(c)). Mild stranding of the peritoneum anteriorly.
50%. Serum lactic acid was normal, and serum lipase was unremarkable. The iron profile showed low iron levels 47 μg/dL with normal ferritin levels. B-Type Natriuretic Peptide (BNP) was 15 pg/mL. Initial serum troponin I levels were normal. Multiple serum tumor markers were tested; Carbohydrate Antigen (CA) 19-9 was 13 U/mL, CEA was 4.3 ng/mL, and Cancer Antigen (CA) 125 was 230.1 U/mL (reference: <35 U/mL). A SARS-CoV-2 rapid test was negative. Pericardial fluid analysis revealed a negative fungal culture, no mycobacterial species were isolated after 6 weeks of incubation, and bacterial culture was negative. Pericardial biopsy showed dense fibrosis and mesothelial cell changes, negative for malignancy. Peritoneal fluid analysis showed a SAAG of < 1.1/dL, and the rest of the peritoneal fluid studies were unremarkable. Serum lactate dehydrogenase was 162 U/L. Serum TSH levels were >100 μIU/mL (reference: 0.34-5.6 μIU/mL), serum free thyroxine level was <0.20 ng/dL (reference: 0.58-1.64 ng/dL), and total T3 level was <0.2 ng/mL (reference: 0.7-2.1 ng/mL). Serum thyroglobulin level was less than 0.4 ng/mL. Serum antithyroglobulin antibody level was 61U/mL (reference < 1). Pelvic vaginal ultrasound did not reveal any signs of ovarian mass or uterine pathology. The serum rheumatoid factor was negative. Serum ANA was negative. Serum ceruloplasmin and serum copper levels were normal. Epstein-Barr virus IgM and IgG were negative. Coombs’ test was negative.

1.5. Therapeutic Intervention. Postprocedure, the size of the pericardial effusion remained stable. The condition was complicated by left-sided pneumothorax, which was considered a postprocedure complication, and required chest tube placement and admission to the critical care unit, where she was monitored. For hypothyroidism, the patient was started on thyroid replacement therapy. On day 1, a paracentesis was performed with removal of 3 liters of fluid from the abdomen. The patient was closely monitored, and she
remained hemodynamically stable on day 2; the pneumothorax was resolved with subsequent removal of the chest tube, and the patient was downgraded to medical floor for further medical care. The patient was later discharged home on levothyroxine with strict recommendations on the importance of adherence and outpatient follow-up.

1.6. Follow-Up and Outcomes. A close follow-up of our patient in the outpatient setting showed normal levels of TSH with no signs of recurrent malignancy on follow-up ultrasound of the neck. Follow-up transthoracic echocardiogram 4 weeks later showed improved LV and RV systolic function with improved LVEF with mild pericardial effusion and no evidence of pericardial effusion (Figure 5). Her CA-125 levels were trending down to 124.8 U/mL, and the patient reported no further symptoms on adherence to thyroid replacement therapy. An outpatient PET scan with the oncology workup returned negative (Table 1).

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Patient undergoes surgical pericardial window, complicated postoperatively by left-sided pneumothorax that required chest tube placement. Thyroid replacement therapy started</th>
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<tr>
<td>Day 1</td>
<td>Paracentesis performed, with removal of 3 liters of fluid</td>
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<tr>
<td>Day 2</td>
<td>Resolution of pneumothorax with removal of the chest tube</td>
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<td>Day 5</td>
<td>Discharged home on strict instructions to adhere to thyroid medication and follow-up with cardiology, obstetrics and gynecology, and endocrinology</td>
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<td>Day 37</td>
<td>Outpatient follow-up showed downtrending of CA-125 levels. Follow-up echocardiogram revealed no recurrence of pericardial effusion. Thyroid hormone levels were within the normal range</td>
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Figure 4: Transthoracic echocardiogram on day 1. The left ventricle has normal size. There is diffuse mild hypokinesis, LVEF is 45-50%. The right ventricular free wall appears thickened and echogenic. There is a small pericardial effusion. (a) Apical 4-chamber view and (b) parasternal long-axis view.

Figure 5: Transthoracic echocardiogram 4 weeks since admission. The left ventricle has normal size. LVEF is 55-60%. LV strain is -19%. The right ventricle free wall is thick, and mitral valve leaflets are thickened. Small-to-moderate circumferential pericardial effusion. There is no evidence of tamponade. (a) Apical 4-chamber view and (b) parasternal long-axis view.
complication of hypothyroidism, the suspicion for hypothyroidism was low and other causes needed to be excluded. Our patient’s condition coupled with elevated levels of CA-125 warranted a workup for ovarian cancer as hypothyroidism has also been rarely associated with elevated CA-125 levels, with one case reported in Japan in 2007 [5].

CA-125 was first described in 1981 by Bast et al. as a glycoprotein raised in 90% of advanced ovarian tumors and has since been used prospectively as a marker for therapeutic efficacy and disease monitoring among ovarian cancer patients but has not been used for screening for ovarian cancer due to inadequate sensitivities, as proven by previous studies [6]. It is rare for hypothyroidism to be correlated with elevated levels of CA-125 [4], with the exact mechanism not being identified yet. One hypothesis explains that the elevation of CA-125 occurs in cases of stretching of the peritoneum with ascitic fluid accumulation, and elevated CA-125 can reach levels comparable to those in ovarian carcinoma; such correlations have been seen in nephritic syndrome and liver cirrhosis, as described by Castro et al. [7]. Another hypothesis is the elevation of CA-125 due to pericardial effusion with delayed clearance of CA-125 in hypothyroid states, with the possibility of CA-125 being related to the severity of hypothyroidism-associated pericardial effusion. A study done by Hashimoto et al. in 1989 showed an inverse relationship between the levels of T4 concentration in abnormal thyroid states and CA-125 [8, 9].

Typical features of myxedema ascites include long duration of hypothyroidism and rapid resolution of ascites following thyroid hormone replacement therapy. In cases of ascites, the diagnostic workup includes paracentesis to analyze the ascitic fluid and to narrow the differential diagnosis, which can be divided into high protein ascites, which usually includes peritoneal malignancies, tuberculous peritonitis, pyogenic peritonitis, and pancreatic ascites, and low protein ascites, which is correlated with liver cirrhosis and congestive heart failure [10].

Peritoneal malignancy must be suspected when the composition of ascitic fluid and ultrasonography are not consistent with portal hypertension. Although in our case, we detected an elevated CA-125, workup for peritoneal malignancy and ovarian carcinoma was done while restarting thyroid hormone replacement therapy, performing a pericardial window for cardiac tamponade and paracentesis for ascites with a positive response noted in the patient’s condition. When the initial workup for malignancy came back negative, the definitive answer would come in the outpatient follow-up setting, where close follow-up and patient adherence to her thyroid medication led to complete resolution of her presentation with no recurrence, and no evidence of peritoneal malignancy was found as well as excluding all other causes.

Early diagnosis of the causes of ascites and cardiac tamponade would prevent the inappropriate use of other management modalities such as frequent paracentesis, liver biopsies, and in cases of failure of diagnosis an exploratory laparotomy [5]. However, not all cases of hypothyroidism-associated ascites present with a SAAG < 1.1, as Oey et al. [4] presented in their study review that the patient can also present with a SAAG > 1.1. Therefore, levels of SAAG are
variable, and neither high nor low SAAG has shown to be a constant feature of myxedema ascites.

Adequate history, physical examination, and guideline-directed management are essential for the early diagnosis of cardiac tamponade and myxedema ascites. Although the condition is rare, it is easily reversible and avoidable with thyroid hormone replacement therapy.

We report our experience to shed light on the importance to exercise caution when analyzing elevated tumor markers in patients with abnormal thyroid hormone levels and to consider the thyroid to be correlated with elevated CA-125 and fluid overload when other devastating causes have been ruled out without having to perform unnecessary invasive procedures. More studies are still needed to understand the mechanisms of pericardial effusion and elevated CA-125 in hypothyroidism.

Additional Points

Patient Perspective. The patient was contacted and declined to share her perspective on the case.

Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Consent

Verbal informed consent was obtained from the patient for her anonymized information to be published in this article.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

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References