

## Use of Combination of Oral Levothyroxine and Liothyronine in Severe Hypothyroidism With Massive Pericardial Effusion

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### Abstract

Thyroid hormone plays an important role in cardiovascular function. Pericardial effusions are commonly seen in cases of severe hypothyroidism. However, large to massive pericardial effusions with cardiac tamponade are exceptionally rare.

Herein, we present two cases of severe hypothyroidism with massive pericardial effusion. Our first case demonstrates that a patient with large pericardial effusion can be managed conservatively with aggressive thyroid hormone replacement therapy. In our second case, pericardiocentesis was performed in addition to thyroid hormone replacement therapy as the underlying aetiology of effusion could not be reasonably limited to hypothyroidism.

These two cases served to highlight and demonstrate rapid normalisation of thyroid function test by using aggressive oral thyroid hormone replacement therapy using liothyronine, in combination with levothyroxine, which led to resolution of pericardial effusion and prevent its re-accumulation.

**Key words:** hypothyroid, pericardial effusion, levothyroxine, liothyronine

### INTRODUCTION

Primary hypothyroidism is characterized by decreased levels of thyroxine (T4) and triiodothyronine (T3) with compensatory high levels of thyroid stimulating hormone (TSH).

Overt hypothyroidism is associated with cardiovascular manifestations, which include increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output, atherosclerosis, coronary artery disease, bradycardia and conduction abnormalities. Another cardiac finding is pericardial effusion.<sup>1,2</sup> However, massive pericardial effusion is infrequent in cases of severe hypothyroidism. The incidence of pericardial effusion in hypothyroidism is 3% in the early mild stage and up to 80% in patients with myxedema.<sup>3,4</sup>

Herein, we present two patients with large pericardial effusion associated with severe hypothyroidism.

### CASES

#### Case 1

A 62-year-old Indian female with past medical history of hypertension, obstructive sleep apnea, heart failure and hypothyroidism, presented with dyspnoea. Over the last three years, she presented with multiple decompensations of cardiac failure. An echocardiogram performed during the first hospitalization in 2018 revealed ejection fraction of 50% with minimal pericardial effusion. Her thyroid function test revealed free thyroxine (FT4) level of <3.1 pmol/L and TSH 174 mIU/L. She was started on low dose levothyroxine 25 mcg OD with planned slow upward titration of levothyroxine. Unfortunately, the patient did not follow up regularly and was not compliant with her levothyroxine dose of 150 mcg OD. In October 2020, she presented with overt clinical and biochemical hypothyroidism. She had marked coarse features with dry skin, loss of outer 3<sup>rd</sup> of eyebrow, delayed reflexes, signs of overt heart failure with muffled heart sounds. Her blood pressure was 166/90 mmHg and she was bradycardic with heart rate ranging from 50-60 beats per minute (bpm).

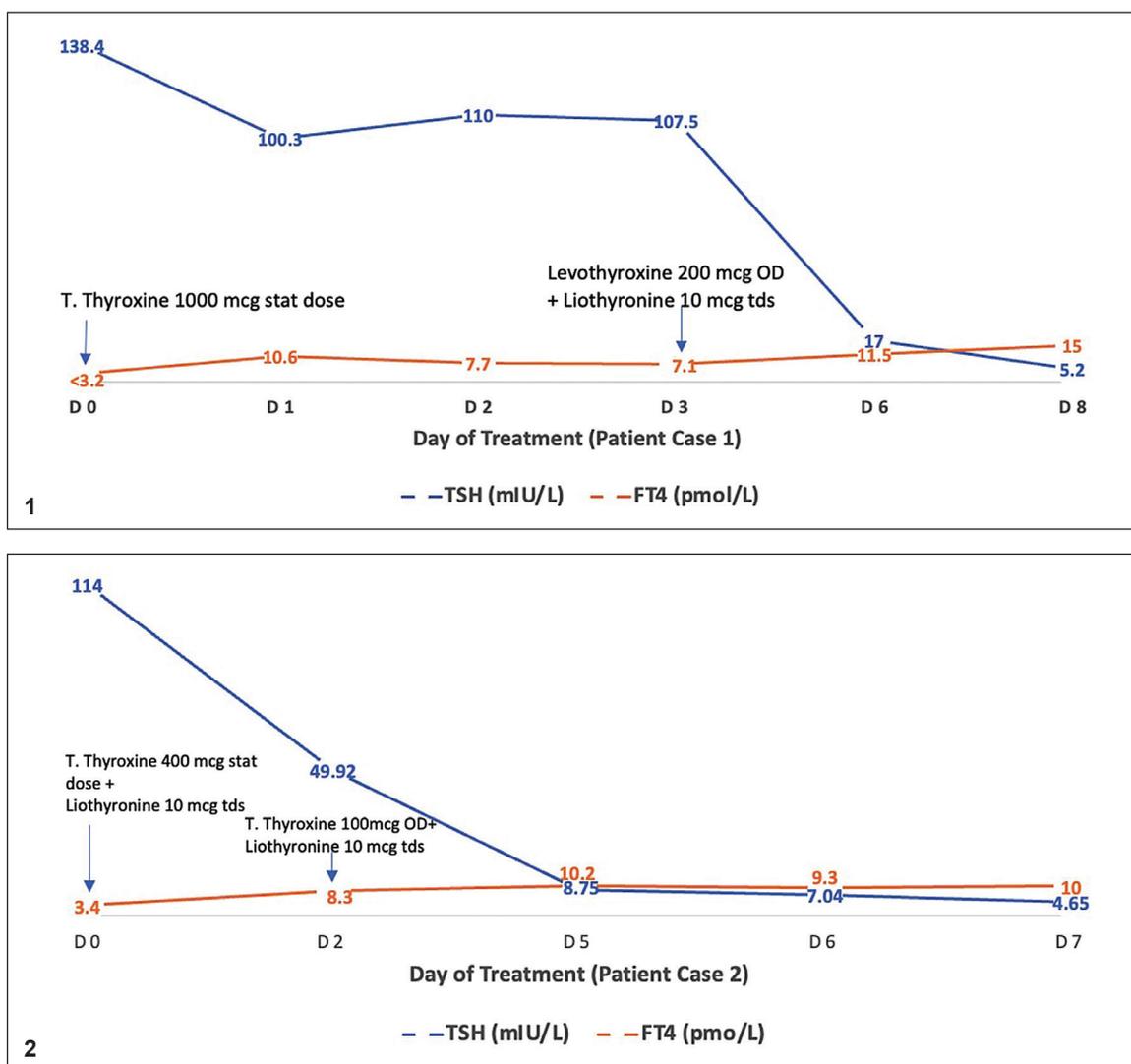
There was no pulsus paradoxus. Her repeat FT4 was <3.2 pmol/L and TSH 138.4 mIU/L. Echocardiogram revealed global pericardial effusion ranging from 9-18 mm, with right atrium and right ventricular collapse.

Thyroxine absorption test was performed, with baseline FT4 <3.2 pmol/L (7.9-14.4 pmol/L), TSH 138.4 mIU/L (0.34-5.6 mIU/L) and FT4 19.2 pmol/L, TSH 166.2 mIU/L four hours after the test, thus demonstrating non-adherence to thyroxine as the cause of patient's persistent hypothyroidism. She was not compliant with her thyroxine regimen due to intermittent forgetfulness, which may have been due to hypothyroidism. She was commenced on levothyroxine 200 mcg once daily (2.2 mcg/kg/dose), in combination with liothyronine 10 mcg thrice daily. Her thyroid function test showed marked improvement on day 2 onwards (Figure 1). On day 5 of combination of levothyroxine and liothyronine therapy, her FT4 was 15 pmol/L (7.9-14.4 pmol/L) and TSH 5.2 mIU/L (0.34-5.6 mIU/L). On day 3, her FT3 level was 6.7 pmol/L (3.8-6.7 pmol/L). Repeat echocardiogram on Day 5 of combination

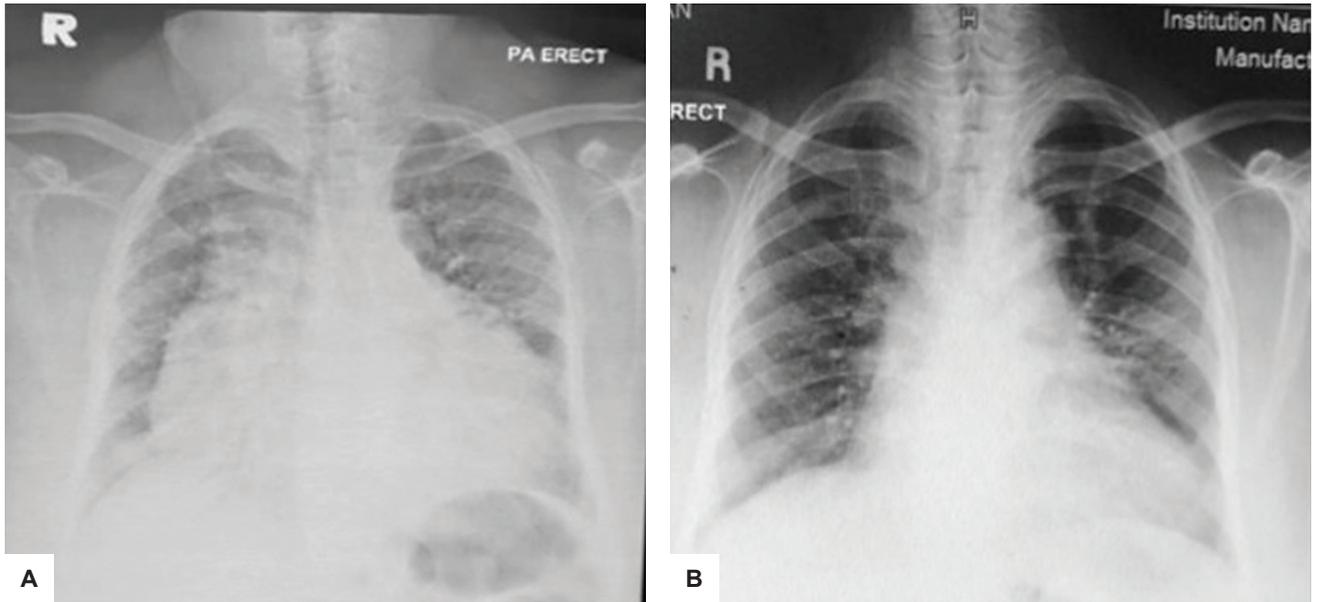
therapy revealed only minimal pericardial effusion ranging from 4-9 mm with no right atrial or ventricular collapse. Repeated chest radiograph and electrocardiogram showed marked improvement post thyroxine hormone replacement therapy (Figures 2 and 3). She was discharged on levothyroxine 300 mcg once daily. Higher dose of levothyroxine was given as the patient was clinically and biochemically in severe hypothyroidism upon presentation. Dose reduction during early clinic review was planned. We carefully counselled the family members on the importance and necessity for directly observed therapy. During follow-up treatment, her thyroxine was down titrated to levothyroxine 150 mcg (1.6 mcg/kg/dose) once daily. She showed marked improvement clinically and biochemically.

**Case 2**

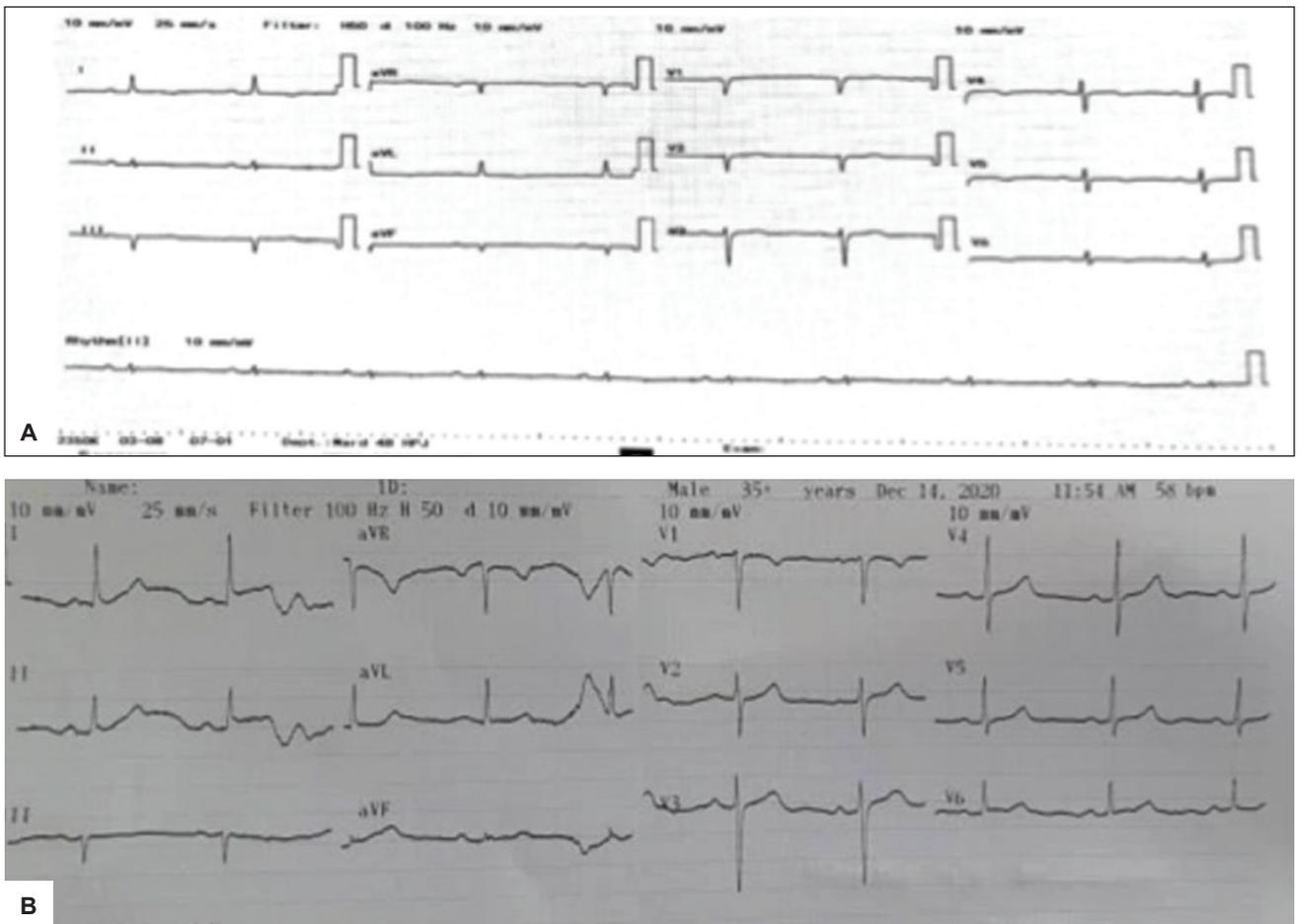
A 65-year-old Malay female with underlying hypertension, type 2 diabetes mellitus, chronic kidney disease stage 3A, history of ischaemic stroke 4 years ago and was semi-



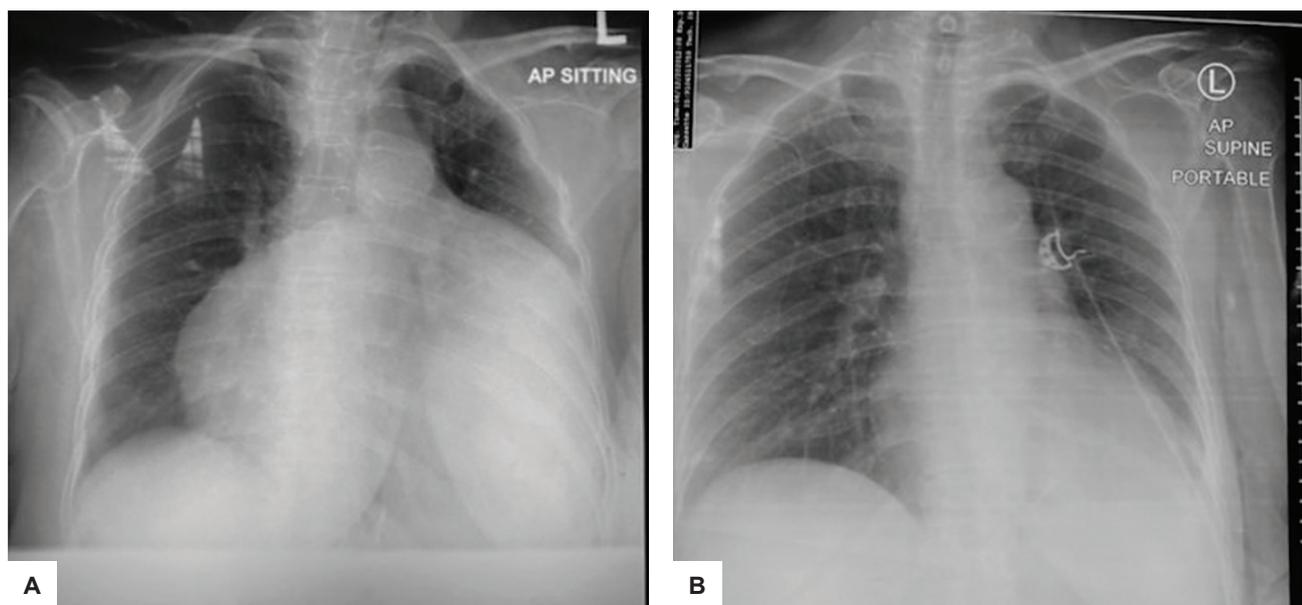
**Figure 1.** Graph (1) showed serial thyroid function tests for Case 1 at baseline and during course of treatment and graph (2) showed serial thyroid function tests for Case 2 at baseline and during course of treatment.



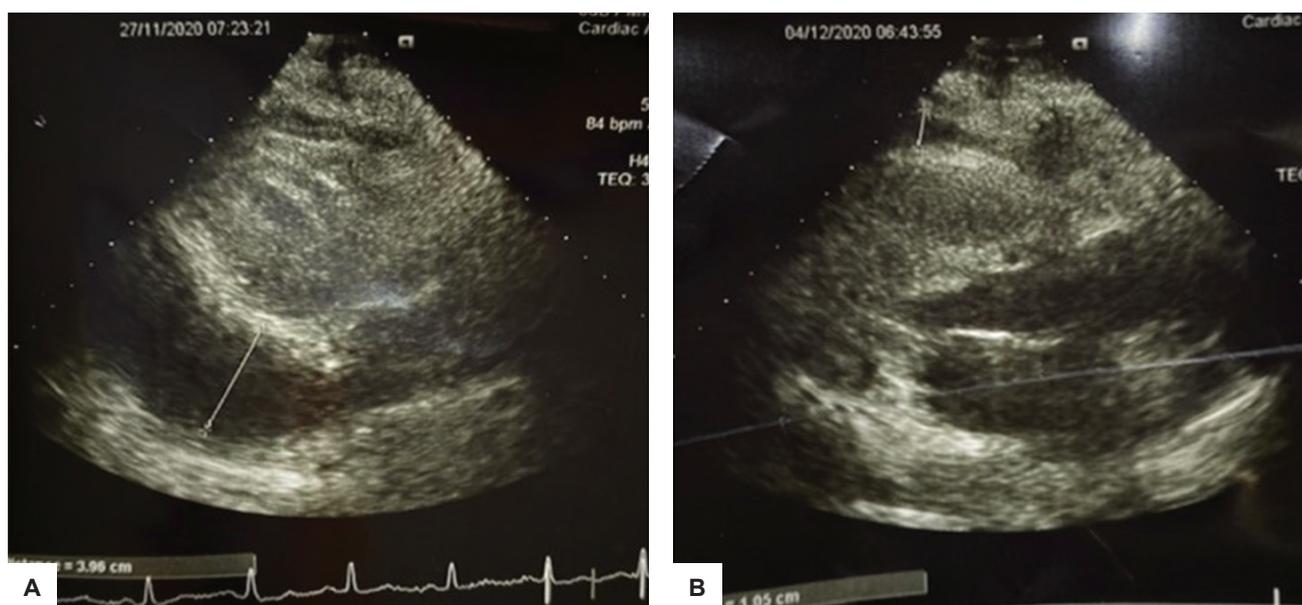
**Figure 2.** (A) PA erect chest radiography of Case 1 demonstrating cardiac shadow with globular appearance. (B) Chest radiography revealing reduction in cardio-thoracic ratio post commencement of thyroxine replacement therapy.



**Figure 3.** (A) Electrocardiogram of Case 1 upon presentation revealing low voltage QRS complexes. (B) Electrocardiogram of Case 1 post thyroid hormone replacement therapy.



**Figure 4.** (A) Chest radiograph of Case 2 showing cardiomegaly with globular enlargement. (B) Chest radiograph post pericardiocentesis showing resolution of pericardial effusion.



**Figure 5.** (A) Transthoracic echocardiogram parasternal long axis view of Case 2 demonstrating pericardial effusion of 3.96 cm. (B) Transthoracic echocardiogram parasternal long axis view showing reduction in pericardial effusion size.

dependent for activities of daily living. She presented with complaints of dyspnoea of 1 year duration. Otherwise, she had no chest pain, no palpitation, no constipation, no weight gain. There was no history of pulmonary tuberculosis contact and no family history of malignancy. On physical examination, she had coarse, dry skin with slow mentation and obvious delayed relaxation of deep tendon reflexes. She was hemodynamically stable with blood pressure of 139/86 mmHg, absence of pulsus paradoxus or bradycardia (pulse rate 84 bpm). On auscultation, heart sounds were muffled. Respiratory examination was unremarkable. There was a 3 cm firm and mobile submandibular swelling with no goitre or surgical scar in the neck. Fine needle aspiration cytology of the submandibular swelling was

performed and reported to have features of sialadenosis. Gynaecological assessment did not reveal any gynaecology pathology.

Blood investigation showed severe hypothyroidism with FT4 3.4 pmol/L (11.5-22.7 pmol/L) and TSH 114.47 mIU/L (0.55-4.78 mIU/L). Her initial electrocardiogram showed low voltage complexes with electrical alternans. Chest radiograph showed massive cardiomegaly (Figure 4). Echocardiogram revealed large global pericardial effusion ranging from 1.2-3.9 cm but no collapse of right ventricular free wall in diastole with left ejection fraction of 65 % (Figure 5). A provisional diagnosis of primary hypothyroidism with massive pericardial effusion was made.

She was commenced immediately on a single high dose 400 mcg levothyroxine followed by lower daily dose of 100 mcg (1.6 mcg/kg/dose) together with liothyronine of 10 mcg thrice daily. Her TSH decreased by half to 49.92 mIU/L (0.55-4.78 mIU/L), with FT4 of 8.3 pmol/L (11.5-22.7 pmol/L) after two days of combination therapy of levothyroxine and liothyronine, which subsequently normalized after one week of treatment, with TSH 4.65 mIU/L, FT4 of 10 pmol/L (Figure 1). Oral liothyronine was given for 10 days.

Repeat echocardiogram did not show improvement in pericardial effusion and it was decided to proceed with pericardial tapping for diagnostic purpose. One litre of pericardial fluid was drained. Echocardiogram reassessment post tapping showed more than 50% reduction of pericardial effusion, ranging from 5-9 mm, no right ventricular chamber collapse during diastole, with ejection fraction of 69% (Figure 5). Pericardial fluid analysis was reported to be acellular with absence of organisms on gram stain and Ziehl-Neelsen stain for acid fast bacilli (AFB). Fluid biochemistry analysis showed normal total protein of 58 g/L (57-82 g/L) and lactate dehydrogenase of 128 U/L (120-246 U/L). There was no growth on bacterial and tuberculosis culture media of the pericardial fluid. Her electrocardiogram showed normal voltage complexes.

Subsequently, the patient was discharged well with levothyroxine 100 mcg OD (1.6 mcg/kg/dose). During clinic review, she appeared well with no complaints of dyspnoea. Her thyroid function improved further and normalized at the second clinic visit with minimal pericardial effusion on echocardiogram reassessment.

## DISCUSSION

We present 2 cases of severe hypothyroidism with massive pericardial effusion and highlight the haemodynamic stability despite the significant echocardiographic findings. The first case demonstrates that a patient with large pericardial effusion can be managed conservatively with aggressive thyroid hormone replacement therapy. In the second case, in addition to thyroid hormone replacement therapy, pericardiocentesis was performed as we considered the possibility of other etiologies besides hypothyroidism contributing to the persistent pericardial effusion.

Overt hypothyroidism is associated with some cardiovascular manifestations including heart failure, cardiomyopathy, arrhythmias, systemic diastolic hypertension, dyslipidemia, and atherosclerotic disease.<sup>5,6</sup> Hypothyroidism has also been implicated as a primary etiology of pericarditis, pericardial effusion, and, even more rarely, cardiac tamponade.<sup>7,8</sup> 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.<sup>9</sup> These findings were present in

both patients which were confirmed with echocardiogram as gold standard for diagnosis for pericardial effusion.

The pathophysiology of pericardial effusions in hypothyroidism is not completely understood. In hypothyroidism, there is increased permeability of pericardial capillaries to albumin and decreased albumin drainage into the lymphatic vessels. This increases intrapericardial colloid pressure, thus resulting in fluid accumulation in the pericardial space by Starling equation.<sup>10</sup> Increased albumin permeability is proposed to be due to release of histamines by mastocytes induced by the low thyroid state or by the direct effect of hypothyroidism on the endothelial layers of pericardial capillaries.<sup>11</sup> Both cases presented with long standing symptoms prior to admission that led to discovery of massive pericardial effusion. The degree and duration of hypothyroidism seem to be the main determinants of the amount of fluid that accumulates in the pericardial sac.<sup>3</sup> Myxedema-associated effusion can be large, defined as >500 mL or echo-free space greater than 20 mm at its greatest width, but the distensibility of the pericardium and slow rate of fluid accumulation protects against hemodynamic compromise due to cardiac tamponade.<sup>12,13</sup> Our cases did not show hemodynamic instability as well. Contrary to the typical tachycardia, a normal heart rate may be present in hypothyroid mediated tamponade providing a clue to the etiology of the pericardial effusion.<sup>7</sup>

In case of myxedema-associated pericardial effusion, no particular clinical guidelines are available to direct its evaluation and treatment. Baldwin et al., suggested that once the diagnosis of hypothyroidism is determined to be the most likely etiology of pericardial effusion, hemodynamic stability should be carefully confirmed by physical examination, including use of manoeuvres to elicit presence of pulses paradoxus.<sup>14</sup>

Echocardiography in both cases demonstrate echocardiographic features with large pericardial effusions that were not associated with hemodynamic instability. In the first case, patient was given combination therapy of levothyroxine and liothyronine, resulting in marked improvement of thyroid function test within short period of time, and the pericardial effusion became minimal after thyroid hormone replacement alone.

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. According to previous studies, complete resolution of the effusion can occur within 4 to 26 weeks without invasive management.<sup>7,15</sup>

Aggressive thyroid hormone replacement therapy using oral liothyronine, in combination with oral levothyroxine were used in both cases, which resulted in rapid normalization of thyroid function. In a case report of hypothyroidism presenting with recurrent pericardial tamponade

rapid reaccumulation of the effusion occurred despite prompt initiation of moderately high-dose levothyroxine treatment. Hence, liothyronine was added in addition to levothyroxine, which appeared to prevent further reaccumulation,<sup>16</sup> as seen in our cases.

In patients with risk factors for coronary artery disease, replacement of thyroid hormone should be done with caution to avoid precipitating acute coronary event especially with combination therapy. Our patients were monitored closely in Coronary Care Unit and medical ward with acute care setting, for new symptoms, arrhythmia and heart failure.

Liothyronine is more rapidly metabolised and has a more rapid effect than levothyroxine. Liothyronine may be used in severe hypothyroid states when there is a possibility that thyroxine conversion to triiodothyronine may be decreased.<sup>17</sup> Levothyroxine alone is the usual treatment for hypothyroidism and is used to replenish the thyroxine pool. It has a half-life of 7 days compared with the 1-day half-life of liothyronine. Meta-analysis by Chiu et al., concluded that weekly levothyroxine administration may be a feasible alternative for hypothyroid patients, particularly when adherence is a concern.<sup>18</sup>

The European Society of Cardiology guidelines for diagnosis and management of pericardial disease suggest that if a specific aetiology 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.<sup>19</sup> In our second case, pericardiocentesis was performed as the underlying etiology of effusion could not be reasonably limited to hypothyroidism.

It is important to note that major actions of thyroid hormone are mediated by binding to a receptor (TR) in the nucleus of target cells. The TR isoforms (TR $\alpha$ 1, TR $\alpha$ 2, TR $\beta$ 1 and TR $\beta$ 2) differ in their distributions in tissues. In comparison with narrow variations of thyroid hormone in a normal individual, the population normal ranges are broader.<sup>20</sup> Therefore, a numerically normal thyroid function test does not necessarily equate to euthyroidism in all tissues. It is important to also assess symptoms clinically despite normal laboratory results.

## CONCLUSION

Pericardial effusion secondary to hypothyroidism will resolve with thyroid hormone replacement therapy. Pericardiocentesis should be reserved for cases requiring diagnostic sampling or for rare cases with evidence of cardiovascular compromise. Combination of levothyroxine and liothyronine therapy can be considered if rapid treatment of hypothyroidism is required and for resolution

of severe pericardial effusion in patients without cardiovascular compromise.

## Ethical Consideration

Patients' consents were obtained before submission of the manuscript.

## Statement of Authorship

The authors certified fulfilment of ICMJE authorship criteria.

## Author Contribution Statement

PSW, SWL, CVT, MM, ZH conceived the study; developed the methodology; verified research outputs; conducted the research; provided the study materials; reviewed and edited the manuscript; presented the data; supervised and coordinated the research activity planning. PSW developed the software. PSW and SWL synthesized and curated the data and prepared the original draft.

## Author Disclosure

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