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A Case Report of Hypothyroidism and Pericardial Effusion

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Abstract

The pericardial sac is made of two layers: the visceral and parietal pericardium. Located between these two layers, the pericardial cavity is found. It contains around 15 to 50 mL of a liquid secreted by mesothelial cells. Pericardial effusion is described as the accumulation of liquid within the pericardial cavity, exceeding the previous mentioned quantity. It has multiple causes, such as malignancy, infectious origins, inflammation, and others, such as hypothyroidism. One of the multiple clinical manifestations associated with hypothyroidism is pericardial effusion. It is related to the severity and duration of the disease, being more frequent in congenital hypothyroidism or cases of a long history of hypothyroidism, as well as clinical hypothyroidism. It can present a clinical challenge mainly due to the discordance between the total volume of the effusion and the clinical symptoms shown by the patient. The main objective of this work is to present a case of a forty-two-year-old male with hypothyroidism-associated pericardial effusion which resolved satisfactorily with hormone replacement therapy.

Keywords

Hypothyroidism, Pericardial Effusion, Echocardiogram, Levothyroxin

1. Introduction

In 1656, English anatomist Thomas Warton names "thyroid", which means "shield-like", to a bilobulated gland located under the larynx and in front and both sides

of the trachea [1].

Zondek, in 1918, described a patient with some characteristics matching a mix edematous heart: dilated cardiac silhouette, low cardiac voltage and slowed cardiac activity. Triiodothyronine was discovered by Pitt-Rivers and Gross in 1952, while its endogenous production was described by Ingbar, Sterling, and Braverman in 1970. Conliffe isolated thyroxine in 1963. In 1971, Mayberry and Hershman simultaneously described the tyrotrophin to diagnose hypothyroidism [2].

Triiodothyroinine (T3) and thyroxine (T4) occurs withind the thyroid gland. T4 is the main product of such synthesis, having no biological effect. T4 to T3 conversion does not happen within the myocyte. About 85% of the total concentration of T3, which is biologically active, is derived from peripherical conversion of T4 by an enzyme named 5'-monodeiodinase, mainly occurring within the liver, kidneys, and skeletal muscle. Both T4 and T3 circulate almost entirely (90%) bound to proteins. The remaining 5% circulates freely. T3 is the biologically active hormone within the cardiac myocyte [1] [2].

Thyroid hormone synthesis is regulated by a negative feedback mechanism in which the hypothalamus-hypophisis-thyroid axis is involved. The hypothalamus secretes thyrotrophin releasing hormone (TRH), which stimulates the hypophysis to secrete thyrotrophin (thyroid stimulating hormone, TSH). TSH stimulates the thyroid gland toi produce and secretes thyroid hormones (TH). Concentration changes of TH are detected by the hypophysis. If there are los levels of TH, it secretes TSH. On the contrary, if the levels are elevated, it lowers secretion. Iodine itself intervenes on TH regulation through a negative feedback mechanism (Wolff-Chokoff effect) with a biphasic effect: on iodine ingestion, synthesis is increased; with increased consumption, synthesis is lowered [2].

Evidence shows that cell membranes contain specific transporting proteins for active hormone. T3 is the main effector of biological actions of thyroid hormones, tissue thermogenesis, effects on diverse cellular proteins' expression, direct effects on the hear, and effects on smooth muscle cells on blood vessels. T3 enters the cell through a facilitated diffusion process, and it seems to penetrate directly into the nucleus without binding to any other protein within the cell. Most of the observations indicate cardiac myocytes can metabolize neither T3 nor T4, so all nuclear effects and genic expressions are due to changes on blood concentrations of T3. All the biological effects of T3 are due to genic and extragenic transcription [1].

Once within the myocyte, T34 interacts with molecules highly associated to chromatin, known as "thyroid hormone nuclear receptors" (RT3). These proteins belong to one of the super family of nuclear receptors. Each of them is a nuclear transcription factor, ligand-dependent, which regulates transcription speed of target genes by binding to a specific sequence of deoxyribonucleic acid (DNA) located on the 5' region flanking said genes. They bind to DNA as monomers, although most of them do so as homodimers or heterodimers made of nuclear receptors of T3 and another thyroid hormone target. These genes code

both regulating and structural proteins, related to cell contraction [1] [2] [3].

Thyroid disfunction is frequent. Hypothyroidism affects around 4.5% of all population (0.3% clinical hypothyroidism and 4.3% subclinical hypothyroidism). It is estimated that it affects around 5% to 8% of adult women, and in lower percentage to men. It is classicaly described as low blood levels of T4 and T3 with increased TSH blood level [4].

Hypothyroid patients can develop protein-rich pericardial effusion, which happens gradually over time. It is more frequent in clinical hypothyroidism than subclinical hypothyroidism. Incidence varies between 30% and 83%. This diverse incidence is attributed to study versatility on disease severity, disease evolution, or selection criteria. Gradual accumulation may explain why the effusion can be of considerable volume without causing cardiac tamponade. The effusion is caused by an increase in capillary permeability, increased albumin distribution volume, and diminished lymph drainage [4].

2. Clinical Case

Forty-two-year-old male, with familiar history of diabetes (both parents, sister, and nephew are known diabetics). Born and resident of the State of Tlaxcala, administrative employee, with previous medical history of smoking, consuming up to 5 cigarettes a day, constant alcoholism up to two years prior to first consult, once a week, occasionally resulting in drunkenness.

The patient presents to clinic complaining of hypersomnia, sensation of nasal obstruction, and snores of three months of evolution. He referred constipation, cold intolerance, dry skin, bradylalia, and high-effort dyspnea. On physical examination, the patient is found awake, oriented, cooperative, bardylalic and without neurological deficit. Pharynx was found normal, and thyroid gland was not palpable. Lungs were found clear, without aggregated sounds. Precordium examination revealed rhythmic cardiac sounds, with adequate intensity and tone, without murmurs. The abdomen was found to be globose due to adipose panicle, with normal peristaltic sounds. Lower extremities were found without edema, muscle stretching reflexes were found to be normal. Initial lab tests reported a normal blood count, blood glucose of 112 mg/dl, urea 25.7 mg/dl, BUN 12 mg/dl, creatinine 1.1 mg/dl, total hypercholesterolemia, and elevated LDL levels. Chest X-ray revealed grade IIII cardiomegaly and suggestive water bottle image. EKG revealed a right-axis deviation. Considering all the reported history and the evidence found both on the EKG and chest X-rays, a transthoracic echocardiogram and thyroid function tests were ordered. Thyroid function tests reported the following levels: TSH 73.45 *u*UI/mL, T4T 1.48 *u*g/dL, T4L 0.08 ng/dL, T3T 0.91 ng/dL, T3L 2.51 pcg/mL. With these results, medical treatment consisting on 100 mcg/day of levothyroxine was prescribed. Two weeks after initiating treatment, TSH levels descended to 35.93 *u*UI/mL, so it was decided to increase levothyroxine dosing up to 125 mcg/day. A new lav determination was realized on April 2018, reporting TSH levels of 2.91 *u*UI/mL (**Table 1** shows the

complete lab results). Transthoracic echocardiogram was performed on February 28th, 2028, reporting right ventricle hypertrophy, right atria enlargement, left ventricle systolic and diastolic normal function, ejection fraction of 68%, conserved right ventricle systolic function, 60% of right ventricle ejection fraction, and a pericardial effusion of 1264 ml without cardiac tamponade was observed. Three months later, a new echocardiogram was performed, but there was no evidence of pericardial effusion (Figures 1-3).

Currently, the patient is found asymptomatic and on a 150 mcg/day levothyroxine prescription.

Table 1. Shows laboratory results.

	Lab results				
	Jan., 24, 18	Jan., 30, 18	March., 6, 2018	April., 10,18	June., 26, 18
Hb	15.8 g				
Hto	51.80%				
VMG	93.2 FL				
MCH	30.8 pg				
MCHC	33g/dL				
RDW	15.80%				
Leukocytes	5300				
Platelets	151,000				
Glucose	112 mg/dL				
Urea	25.7 mg/dL				
NUS	12 mg/dL				
Creatinine	1.11 mg/dL				
Cholesterol	236 mg/dL				
C-HDL	52 mg/dL				
C-LDL	139 mg/dL				
Triglycerides	156 mg/dL				
TSH		73.45 uUI/mL	35.93 uUI/mL	2.91 uUI/mL	5.54 uUI/mL
T4T		1.48 ug/dL	12.31 ug/dL	16.38 ug/dL	18.88 ug/dL
T4L		0.08 ng/dL	0.56 ng/dL	0.98 ng/dL	0.92 ng/dL
T3T		0.91 ng/dL	2.27 ng/dL	2.14 ng/dL	1.78 ng/dL
T3L		2.51 pg/mL	3.37 pg/mL	4.51 pg/mL	5.56 pg/mL

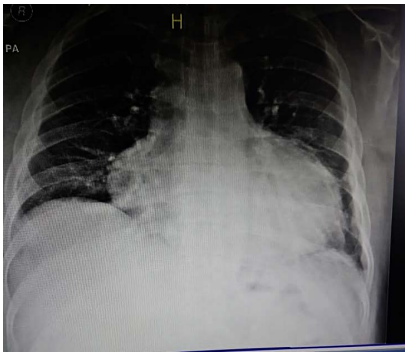

Figure 1. Chest X-ray.

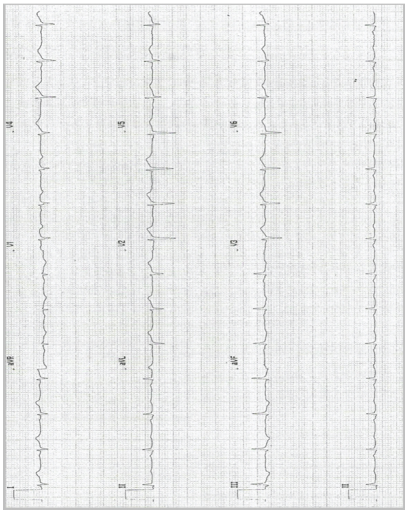

Figure 2. Electrocardiogram.

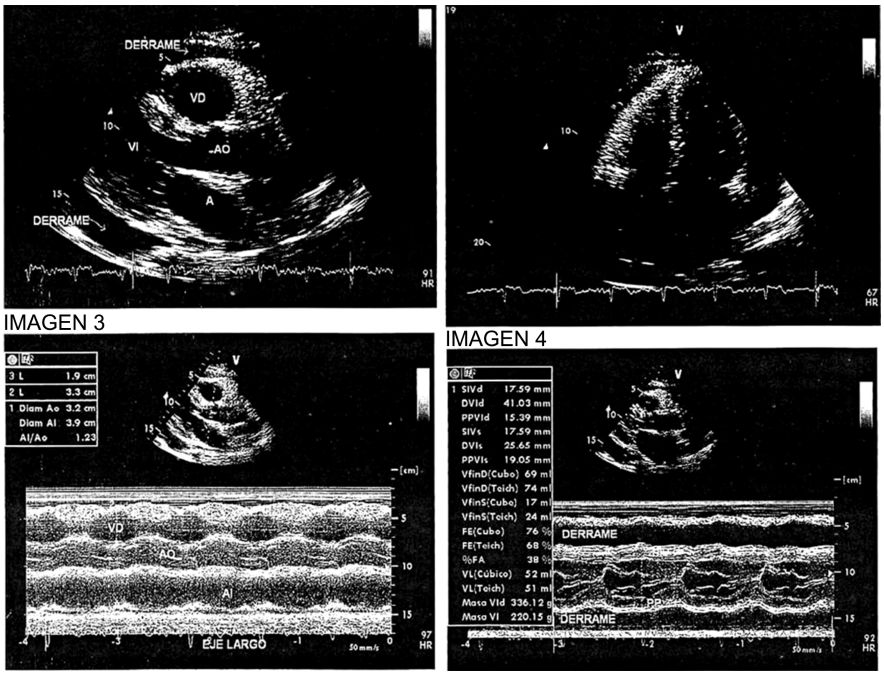

Figure 3. Echocardiography.

3. Discussion

Pericardial effusion is described as the abnormal accumulation of fluid within the pericardial cavity. Such liquid can be either exudate, transudate, pyopericardium, or hemopericardium [5].

A fibroelastic sac contains the heart and proximal great vessels. The pericardium anchors the heart to the mediastinum, provides lubrication, and acts against infection and acute distention of the heart chambers. It is made of two fine leaflets: one serous, visceral, and a fibrous, parietal, leaflet. The visceral leaflet is thin and in intimate contact with the epicardium, whereas the parietal pericardium is an external layer in contact with the thoracic wall [5] [6].

It contains around 15 to 40 mL of a liquid secreted by mesothelial cells through a plasma ultrafiltration process done by the pericardic capillaries, and drained mainly by the lymph system, propelled by an increase of pericardic pressure. The accumulation of liquid within the pericardic cavity exceeding the values is known as pericardial effusion [5] [6] [7] [8]. It can consist of more than 1000 cc of fluid and can cause an increase of pericardial pressure (normal values: −5 to +5 mmHg), decreasing cardiac output and causing cardiac tamponade. Pressure-volume relation determines the hemodynamic effects of pericardial effusion [7].

Numerous causes can produce pericardial effusion. Any process which causes inflammation, wounds, our diminishes lymph drainage can cause it. The causes can be divided into inflammatory and non-inflammatory [6] [7].

Idiopathic pericarditis, usually of viral origin, is the most common cause of pericardial effusion related to inflammation in the United States and Western Europe. Although histological, cytological and immunohistochemical evaluations are required, including detection of viral nucleic acids, to determine the origin of the effusion, these tests are normally not required. Serological routines are not currently recommended [6].

If the patient is immunocompromised, or previous medical history suggests infection by bacteria or fungi, pericardial effusion culture is essential to guide medical treatment. Effusions caused by bacteria or fungi are typically exudates, and in sever cases can be purulent effusions [6].

Tuberculosis in developing countries is the most common cause of pericardial effusion. It is usually related to a 17% to 40% mortality rate within 6 months after diagnosis. Patients under suspicion of tuberculosis should be studied for extracardiac tuberculosis. These tests can be obtained either by pericardiocentesis or pericardial biopsy to be sent for culture or PCR testing.

In some cases, pericardial effusion might be the first manifestation of malignancy. Nonetheless, in almost two thirds of all patients, malingnat cells might not be present. Extracardiac cancer is more frequent than primary cardiac malignancies, with a higher incidence of lung cancer, breast cancer, or lymphoma. Mesothelioma or angiosarcoma might rarely happen. Pericardial effusion might also present after bone marrow transplant or mediastinum radiation [6] [7].

Pericardial effusion might present after cardiac injury, following myocardial

infarction. It is believed that early presentation occurs due to myocardial necrosis extending to the pericardium, whereas late presentation (Dressler's Syndrome) might present from weeks up to two months after infarction. It is believed to be caused by autoimmune reaction to cardiac antigens. Some procedures, such as pericardiotomy or other electrophysiological procedures which can cause myocardic or coronary perforation might cause pericardial effusion [7].

Pericardial fluid might accumulate in non-inflammatory processes, such as in elevated venous pressure cause by heart failure and liver cirrhosis. In such cases, reduces reabsorption might cause transudative effusions. Frequently, patients do not refer symptoms derived by pericardiac effusion. The effusion is accidentally found through imaging studies [6].

Pericardial effusions can also be caused by blunt forces or penetrating trauma to the thorax, such as in aortic dissections. These can extend up to the aortic root, causing retrograde bleeding within the pericardium. In cases of acute hemorrhage due to fast fluid accumulation, cardiac tamponade develops despite small volumes of fluid [7].

Metabolic diseases can cause pericardial effusion with signs and symptoms that may direct the diagnosis. Uremia can cause pericardial effusion with hemorrhagic fluid and fibrinous exudates, adhered to the pericardium. In such cases, hemodialysis is the main treatment. These situations are less frequent as time goes by, mainly because of early prescription of kidney function replacement therapy [5] [6] [7].

Hypothyroidism has been described as a cause of pericardial effusion. It is a common finding in patients with primary hypothyroidism. Pericardial effusion secondary to hypothyroidism might present a diagnostic challenge due to the discordance between the fluid's volume and clinical symptoms presented by the patient [8].

Any defect of the hypothalamus-hypophisis-thyroid axis can result in the development of hypothyroidism. Low T4 blood levels, along with TSH elevation, suggest hypothyroidism. Hypothyroidism can cause a myriad of symptoms, including weight gain, fatigue, cold intolerance, constipation, dry skin, edema, muscular weakness, and diminished deep tendinous reflexes. It is associated with some cardiovascular findings such as increased systemic vascular resistances, diminished cardiac contractility, diminished cardiac output, atherosclerosis, coronary artery disease, bradycardia, and conduction abnormalities. One of the main cardiac diseases associated to this clinical entity is pericardial effusion. Before, incidence was estimated to be from 30% to 80%, mainly because a correct diagnosis was delayed. Currently, incidence is located between 3% to 6% due to early hypothyroidism diagnosis [9] [10]. Khalelli and cols, in 1982, found an incidence between 30% to 78% in different series. In their study group, 5 out of 6 patients presented pericardial effusion [11]. It is associated with disease severity, being more frequent in congenital hypothyroidism or long-evolution hypothy-

roidism. There is no correlation with blood levels of thyroid hormones or TSH [12] [13] [14] [15]. Even though most cases have been described in clinical hypothyroidism, Dattilo's group reported a single case of pericardial effusion in subclinical hypothyroidism, describing a 41-year-old patient with increased TSH levels and normal hormone thyroid levels [16]. In a study performed by González, out of 42 patients with untreated hypothyroidism, 19 patients presented clinical hypothyroidism and 23 subclinical hypothyroidism. Pericardial effusion was more frequently observed in the first group, higher levels of TSH were observed in those patients where the effusion was present than in those in those where there was no effusion [17]. Aside from pericardial effusion, other serous effusions have been documented, such as pleural effusion and ascites. Alljadir, in a study performed in Iraq, reported 9 out of 22 patients with pericardial and pleural effusion, and ascites [18] [19]. Kumar described a 60-year-old patient with these three previously mentioned entities coexisting at once [20]. It has been described it might be accompanied with acute kidney injury, such as Kaplan demonstrated on a Turkish patient [13].

The mechanism by which exudative effusions are caused is by the extravasation of hygroscopic mucopolysaccharides within the pericardial space, along with an increase on capillary permeability, decreased lymph drainage, and increased salt and water retention, along with increased albumin volume distribution [4] [5] [10] [19] [20] [21]. Usually, the pericardium is impermeable to proteins. Physiological pericardial fluid is made by the trasudate of epicardial capillary arterioles. A part of this fluid can be reabsorbed within the venules of such capillaries, and the rest can be drained by the parietal pericardium's lymph vessels. In hyperthyroidism, increased albumin permeability along pericardial capillaries, along with decreased albumin drainage within lymph vessels, increases colloid osmotic pressure and reduces the pressure gradient (between the pericardium and the pericardial space), resulting in the accumulation of fluid within the pericardial space according to Starling's law. The etiology of increased albumin permeability is proposed to be related to histamine liberation induced by hypothyroidism, or by a direct effect of hypothyroidism onto the pericardial capillaries along the pericardial leaflets. An additional theory to the decreased lymph drainage is that hypothyroidism induces a reduction of circulating catecholamines (whose role is to increase lymph flow) [8]. The effusion's volume is directly proportional to the duration and severity of the hypothyroid state. However, some authors point that there is no relation to the duration of the disease [5] [14] [15] [17].

It has been observed as well that pericardial effusion present in hypothyroidism rarely causes cardiac tamponade. However, many authors have reported the presence of this entity, even as a debuting clinical presentation, such as the case reported by González Villena in a hospital of the State of Mexico [22]-[33].

Pericardial effusions, by themselves, are symptomatic unless they cause cardiac tamponade, presenting with dyspnea, tachycardia, tachypnea, hypotension,

muffled heart sounds, paradoxical pulse, and elevated jugular venous pressure. Many patients with cardiac tamponade may present with coexisting pericarditis and refer typical thoracic pain and pericardial rub. Not infrequently, patients may experience upper right quadrant pain due to hepatic congestion. They may present signs and symptoms of one of the many causes which may provoke pericardial effusion, just as in the described case the symptoms strongly suggested hypothyroidism. Without cardiac tamponade, cardiovascular examination is normal except in those cases in which there are large volumes of effusion. Heart sounds might become muffled and it may be difficult to palpate the apex pulse [5] [7] [8]. In the reported case, despite the effusion's volume was estimated to be more than 1000 cc, cardiovascular physical examination did not provide relevant data.

Due to patients suffering of pericardial effusion might report thoracic pain or dyspnea, chest X-rays must be obtained. However, they might show no abnormalities. In large-volume effusions, cardiac silhouette might be rounded, usually described as a bottle. In the reported case, cardiomegaly and bottle sign could be observed. Chest X-ray findings, though, lack sensibility and specificity. Cardiothoracic index is higher in 55% of 70% of all patients, but only in 67% of patients is higher than 75% [5] [6].

Echocardiogram is the preferred diagnostic tool, being sensible to diagnose pericardial effusion and cardiac tamponade. It provides useful information about the volume, localization, and hemodynamic effects of the effusion. Located between the epicardium and pericardium, many effusions are anechoic, but a complex effusion may present with a more heterogeneous appearance. Pericardial fat is more hyperechoic and moves along the myocardium during cardiac cycle. Sometimes, it is difficult to distinguish between pleural and pericardial effusion. Using the descending aorta on a parasternal long axis might serve as a reference point. Pericardial effusion normally is located anteriorly, between the aorta and the myocardium, whereas pleural effusion remains posteriorly to the aorta [6] [7].

If the pericardial effusion can be appreciated during systole, it is a physiological effusion. If it can be appreciated during the cardiac cycle, final dimensions after diastole might help determine the volume following the classic determination: small <10 mm, big 20 - 25 mm, and excessively big >25 mm. Using just one dimension might misinterpret the final volume [6].

On non-complicated pericardial effusions, echography is enough to diagnose and to follow up the patient. It can be used to guide pericardiocentesis. Transesophageal echocardiogram is much more precise than transthoracic echocardiogram to determine extension and localization of the effusion. Loculated effusions happen frequently after surgical or percutaneous procedures, or in patients with recurring pericardial disease. They are particularly important because, depending on their localization, they might cause chamber collapse and hemodynamic deterioration even if they are small [6] [7] [8].

Even though 2-D transthoracic echocardiogram is the imaging modality of choice, CT scans might be an important imaging modality when more precision to determine and quantify the effusion is needed, or when the effusion is complex or loculated, or when a blood clot is present. It allows to identify pericardial fat and distinguish pericardial thickening from the effusion. Those effusions that are accompanied by pericardial thickening of more than 4 mm and mediastinal lymphadenopathies are highly suggestive of malignancy. It can finally distinguish pericardial effusion from entities which might simulate pericardial disease, such as complex pericardial effusions, mediastinal abnormalities, lower lobe atelectasis, and external masses which displace the pericardium. It also provides data about the pericardial fluid's composition based on the attenuation coefficient (Hounsfield Units). Effusions with similar attenuation to water (<10 HU) are probably transudates, whereas those with higher attenuation (>60 HU) are probably hemorrhagic in nature. An exudative effusion can typically have intermediate attenuation (10 - 60 HU) [6] [7] [8].

Cardiac MRI has the potential to provide anatomical an hemodynamical information of the pericardium. It is reserved for patients with poor echosonographic window, non-concluding echocardiographic evaluation, evaluation for constrictive pathophysiology, or persistent pericardial inflammation after standard therapy [6].

Pericardiocentesis is not always necessary to establish the cause of the effusion. In many instances, the cause is evident or suggested by clinical history, or might have been obtained by previous diagnostic tests. In the reported case, clinical examination and confirmation through thyroid function tests helped establish the effusion's cause. Fluid analysis generally has low utility to provide a specific diagnosis.

Different authors consider that if the effusion has a specific cause, the most appropriate treatment to the underlying disease is the most appropriate treatment for the effusion [6] [7]. Due to hypothyroidism being a treatable cause of pericardial effusion, even massive effusion, diagnosis should be established, and treatment should be started as soon as possible. Many authors agree on the treatment for pericardial effusion due to hypothyroidism: prescription of levothyroxine [8] [9] [24] [25]. The effusion disappears after appropriate treatment in a time window between one to twelve months, sometimes up to 15 months. The most recommended treatment is based on L-thyroxine. The patient presented in this case responded satisfactorily to thyroid hormone replacement therapy without the need to perform pericardiocentesis despite the magnitude of the effusion. What has been observed in the medical literature was observed on this patient, even if it is just one case. The effusion's remission was achieved after three months of initiating treatment: Control echocardiogram was performed within this time frame, so the authors ignore the exact date of the effusion's remission. In those cases where the patient presents with cardiac tamponade, pericardiocentesis is mandatory. A scoring system developed by Halpern's group

to make the decision to perform pericardiac draining is based on clinical data, echocardiographic hemodynamic evaluation, and the volume of the effusion. The pericardial and myocardial diseases group from the European Cardiology Society has proposed a new step-by-step scoring system for those patients who require pericardiocentesis [11] [15] [22] [23] [24] [28] [34]. The pericardial effusion It can present a clinical challenge mainly due to the discordance between the total volume of the effusion and the clinical symptoms shown by the patient.

4. Conclusion

Pericardial effusion on hypothyroidism is an infrequent entity. Hypothyroid patients might develop a progressive effusion. It is more frequent in clinical hypothyroidism; clinical manifestations are those caused by the underlying disease which caused the effusion. The best diagnostic method is echocardiography. Thyroid hormone replacement therapy is the best option for treatment. With it, the effusion resolves in one to 15 months after being initiated. Pericardiocentesis is only performed if cardiac tamponade is present.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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