# Heart Failure and Short Stature in a 43 year-old male

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**Presentation of the case**

This is a case of a 43-year-old male presenting with short stature and heart failure. The patient was admitted at the medicine ward of the Philippine General Hospital (PGH) for dyspnea. This paper will investigate several issues: differentiating congenital from acquired hypothyroidism, the relationship between hypothyroidism and the cardiomyopathies, and the therapeutic options in patients with cardiomyopathy secondary to hypothyroidism.

The patient had been born full term to a then 31-year-old Gravida 4 Para 3 (G4P3), the 4th of 9 siblings, with an apparently unremarkable delivery at home facilitated by a traditional birth attendant. He was noted to be normal at birth. The patient was allegedly at par with age both physically and mentally until eight years old when he was said to have stopped growing in height. He was brought to a private doctor, whose diagnosis was undisclosed, and he was given medications to increase height, which the patient took for only one month with no improvement. Through the years, the patient was apparently well, although still of short stature, with thick lips, coarse facial features and dry skin. He was notably slow in ambulation. He was said to have bronchial asthma at age 15 years, and since then he had been taking salbutamol tablets occasionally for bouts of dyspnea occurring one to two times annually.

The patient's symptoms started in 2001 when he was reported to have sudden loss of consciousness. During this time, the patient did not have any symptoms of heart failure; no prior seizures, cyanotic episodes, chest pain, headache, or blurring of vision. He regained consciousness shortly after and was brought to a private physician, whose assessment was a "heart problem". He was prescribed unrecalled medications taken for a few months and eventually discontinued when the syncopal episode did not recur.

In the next four years, the patient would develop intermittent, progressive exertional dyspnea and bipedal edema. Later on this would be accompanied by generalized body weakness, anorexia, and constipation, severe enough to require regular laxative use. There was also a report of two more syncopal episodes. He was brought to another doctor in a private hospital where the assessment was still a "heart problem". The patient was again prescribed unrecalled medications and again was lost to follow-up. This time, however, symptoms were persistent. He later consulted at another local hospital, where he was admitted and managed as a case of anemia and bronchial asthma. He was discharged slightly improved after four days, only to have recurrent heart failure symptoms, prompting admission at PGH.

Upon admission the patient was in mild respiratory distress, with stable vital signs and no note of fever. Pertinent physical exam findings included short stature, thick lips, non-pitting periorbital edema, dry skin, a displaced apical impulse, crackles on both lung fields, and bilateral non-pitting bipedal edema. There was also a 3 cm x 3 cm reducible umbilical hernia. However, there was no pallor, no neck vein distention, no apparent congenital malformations, no cardiac murmurs and no clubbing. There was also no note of an anterior neck mass.

Laboratory workup showed cardiomegaly with pulmonary congestion, thoracic dextroscoliosis, and atheromatous aorta by chest radiograph, and left ventricular hypertrophy by 12-lead electrocardiogram (12-L ECG) (Figures 1 and 2), normocytic normochromic anemia (Hgb 90 mg/dL), dyslipidemia, and pre-renal azotemia (serum creatinine 123 mmoL). Electrolytes on admission showed slight hyponatremia, hypokalemia, and hypochloremia (serum Na 136, K 3.35, Cl 86). Blood gases revealed partially compensated metabolic alkalosis with mild hypoxemia. The patient was noted to be hypothyroid based on elevated serum thyroid-stimulating hormone (TSH) and markedly decreased serum free thyroxine (FT4). The exact values are shown in Tables 1 and 2.

Upon admission to the wards, the patient was managed as having congestive heart failure from cardiomyopathy secondary to acquired hypothyroidism. Oral loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, statins, and levothyroxine were started. Electrolyte correction was instituted. The sections of Endocrinology and Cardiovascular Diseases were co-managing the patient together with the General Medicine service.

He soon developed respiratory failure, upon which the considerations were acute pulmonary congestion, nosocomial pneumonia, to rule out an acute coronary event. He was later

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**Table 1.** Initial Laboratory Results

| CBC | | | Blood chem. | | | Urinalysis | | ABG | |
|---|---|---|---|---|---|---|---|---|---|
| | Reference Value | Result | | Reference Value | Result | Color | straw | pH | 7.408 |
| | | | | | | Transp | Clear | pCO2 | 49.1 |
| WBC | 5-10 | 4.5 | RBS | 3.9-6.1 | 6.3 | Sp Gravity | 1.010 | pO2 | 70 |
| RBC | 4-6 | | HGBA1C | 4.27-6.07 | 6.4 | pH | 8.0 | HCO3 | 31.3 |
| HGB | 120-150 | 90 | BUN | 2.6-6.4 | 5.0 | Sugar | NEG | O2 sat | 93.6 |
| HCT | 0.38-0.48 | 0.27 | CREA | 53-115 | 123 | Protein | NEG | FiO2 | 21% |
| MCV | 80-100 FL | | ALB | 34-50 | 32 | RBC | 0-1 | Temp | 36.9 |
| MCH | 27-31 PG | | TAG | 0.34-1.7 | 0.82 | WBC | 0-2 | | |
| MCHC | 320-360 G/L | | HDL | 0.91-1.56 | 0.67 | Cast | | **PBS** | |
| RDW | 11.5-15.5% | | LDL | 1.1-3.8 | 4.21 | Epith cell | Rare | Slight poikilocytosis, acanthocytes, ovalocytes, slight toxic granulation, slight anisocytosis | |
| PLT | 200-400 | Inc | TOTAL CHOL | 4.2-5.2 | 5.25 | Bacteria | Occ'l | | |
| RETIC | 0.005-0.015 | | AST | 15-37 | 95 | Mucus th | Rare | | |
| SEG | 50-70% | 48 | ALT | 30-65 | 91 | Crystals | Rare | | |
| LYMPH | 20-44% | 50 | Alk po4 | | 184 | Am urates | | | |
| MONO | 2-9% | 2 | NA | 140-148 | 136.9 | | | | |
| EO | 0-4% | 0 | K | 3.6-5.2 | 3.35 | | | | |
| BASO | 0-2% | 0 | CL | 100-108 | 86 | | | | |
| BLAST | 0% | 0 | CA++ | 2.12-2.52 | 2.37 | | | | |
| | | | P | | 2.27 | | | | |
| | | | MG++ | 0.74-1 | 0.83 | | | | |

**Table 2.** Thyroid Function Tests

| | Reference Value | Result |
|---|---|---|
| Free T4 | (0.8-2.0) | 0.02 ng/dL |
| TSH | (0.4-6.0) | 24.75 Uiu/ml |

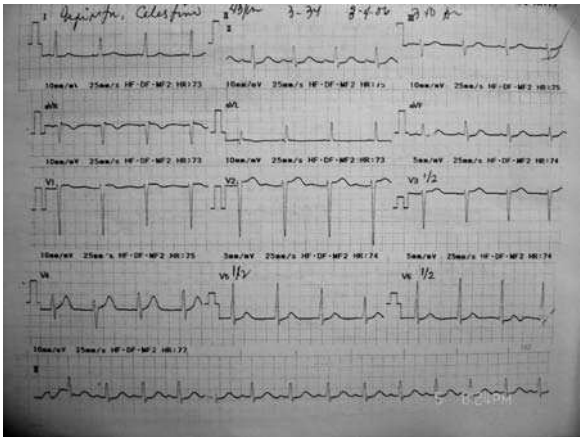

**Figure 1.** Electrocardiogram upon admission

transferred to the intensive care unit (ICU) for ventilatory support and closer monitoring. On bedside cardiac ultrasound, there was a finding of eccentric left ventricular hypertrophy, global hypokinesia with depressed overall systolic function with concomitant spontaneous echo contrast on left ventricular (LV) cavity suggestive of rheologic stasis, the ejection fraction was 25%, with moderate mitral regurgitation, moderate aortic regurgitation with aortic sclerosis, severe tricuspid regurgitation with mild pulmonary hypertension, pulmonary regurgitation, and minimal pericardial effusion or pericardial fat pad. Cardiac enzymes were not consistent with an acute coronary event (Table 3), however, intravenous (IV) heparin (overlapping with oral warfarin) was still given to cover for the presence of a possible LV thrombus as demonstrated by rheologic stasis on cardiac ultrasound. Medications were shifted to IV diuretics and inotropes; oral digoxin was started. IV antibiotics were given for possible pulmonary infection. The patient later on showed improvement, and was eventually weaned off from ventilatory support, extubated, and transferred back to the main ward.

**Table 3.** Cardiac Enzymes

| | Reference Range (mmoL) | Result |
|---|---|---|
| Qualitative Troponin I | | POSITIVE |
| CK-MB | 0-6.0 | 1.14 |
| CK-TOTAL | 21-232 | 543 |

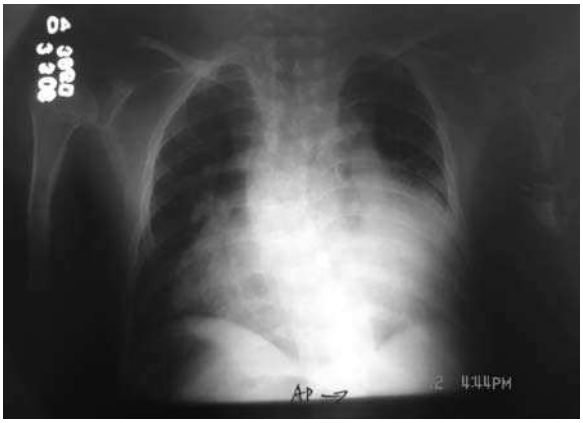

**Figure 2.** Chest radiograph on admission

At the main ward, the patient initially showed improvement. He had been on levothyroxine replacement at 2.6 μg/Kg/day (100 μg per day). Further workup for hypothyroidism showed normal levels of thyroid peroxidase antibody (16.8 U/mL, reference range ≤100 U/mL), not consistent with acquired hypothyroidism secondary to an autoimmune process. He later succumbed to progressive heart failure, eventually expiring from fatal ventricular arrhythmia. Postmortem examination revealed thyroid hypoplasia, short stature, dilated cardiomyopathy in congestive heart failure, with cardiomegaly and myxedematous degeneration of the mitral valve, consistent with primary hypothyroidism.

## Discussion

We are presented with a case of progressive heart failure in an adult patient having short stature and clinical features of hypothyroidism. Ancillary examinations were consistent with hypothyroidism and dilated cardiomyopathy in congestive heart failure. While the fact that the patient reached adult age without significant cognitive disability seems to point more to an acquired cause of hypothyroidism, postmortem examination was consistent with primary hypothyroidism. It is therefore important to analyze several key issues in this case: first, to ascertain the cause of hypothyroidism in this patient; second, to study the relationship between hypothyroidism and the cardiomyopathies; and third, to present therapeutic options in patients with cardiomyopathy secondary to hypothyroidism.

### *Congenital vs. Acquired Hypothyroidism*

The finding of an increased TSH is consistent with primary hypothyroidism, which may be congenital or acquired (see Figure 3). Congenital primary hypothyroidism occurs in approximately one of 4000 live births.[1] The majority of the cases are due to agenesis or dysgenesis of the thyroid gland. One fifth of these hypothyroid newborns have a defect in thyroid hormonogenesis, which leads to goitrous hypothyroidism. In the five genes known to be important for thyroid hormonogenesis, several mutations have been described in the sodium iodide symporter (NIS), the thyroid oxidase 2 (THOX2), the pendrin (PDS), and the thyroglobulin (TG) gene. The most common mechanism to cause dyshormonogenesis is a defect in the thyroid peroxidase (TPO). This membrane-bound, glycosylated, haemoprotein enzyme is located on the apical membrane of the thyroid follicular cell. It catalyzes the iodination of tyrosyl residues and the coupling of iodotyrosyl residues in the thyroglobulin molecule so that triiodothyronine (T3) and thyroxine (T4) are synthesized. The gene coding for TPO is located on chromosome 2 (2p25). It spans about 150 kb and consists of 17 exons, which encode a protein of 933 amino acids. So far, 46 mutations in the TPO gene have been described, resulting in an inactive TPO protein.

Congenital hypothyroidism is caused by thyroid gland dysgenesis in 80-85% of cases.[2] Majority of infants appear normal at birth, later developing prolonged jaundice, feeding problems, hypotonia, an enlarged tongue, delayed bone maturation, and an umbilical hernia. Permanent and severe neurologic damage (cretinism) occurs if treatment is delayed. In acquired hypothyroidism, which is usually the result of autoimmune destruction of thyroid tissue, there is an insidious onset, more consistent with the patient's presentation. Typical signs and symptoms often appear much later during adolescence, including dry skin, decreased sweating, skin thickening without pitting (myxedema), diffuse alopecia, constipation, weight gain, and a hoarse voice. There is also constipation, heat intolerance, sexual pseudoprecocity, and cardiovascular effects including bradycardia, diastolic hypertension, and pericardial effusions. The insidious temporal development of symptoms and level of cognitive function in this patient is more coherent with an acquired cause of hypothyroidism.[3] The presence of antibodies to thyroid peroxidase (TPO) would have confirmed a diagnosis of acquired hypothyroidism. The reason for distinction between these two conditions, however, is purely academic, for clinical management does not differ between the two causes.

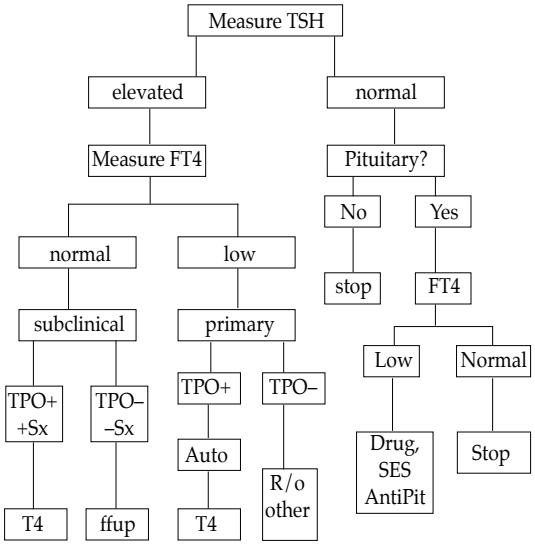


Figure 3. Algorithm for determining the causes of hypothyroidism

### *Hypothyroidism and Cardiomyopathy*

The cardiovascular consequences of hypothyroidism include a reduction in myocardial contractility and pulse rate, manifesting as decreased stroke volume and bradycardia. Increased peripheral resistance may be accompanied by hypertension, particularly diastolic. All these cardiac effects usually improve upon institution of hormone replacement. Though alterations in myosin heavy isoform expression have been documented,[4] cardiomyopathy, as seen in this patient, is unusual.[5]

The cardiovascular manifestations of myxedema were first described by Zondek of Munich in 1918,[6] which included

a low cardiac index, decreased stroke volume, decreased intravascular volume, and increased systemic vascular resistance. He also described other systemic effects such as a decrease in total blood volume as a result of the change in basal metabolic rate, leading to a decrease in free water clearance from decreased renal perfusion causing hyponatremia, and an expended total body albumin distribution. Though Zondek did not include pericardial effusions in his descriptions, this latter phenomenon explained the tendency of patients with hypothyroidism to develop high-protein content effusions in body cavities, including the pericardium. Zondek noted that these manifestations would improve following thyroid hormone replacement therapy.[7,8,9,10]

There have been several case reports describing the occurrence of reversible cardiomyopathy among hypothyroid patients. In 1980, Santos described the presence of global myocardial hypertrophy, predominantly septal,[11] in a patient with primary hypothyroidism. Later, Kotake reported two cases of hypothyroidism with echocardiographic features of cardiomyopathy.[12] Okabe then reported the histopathologic finding of diffuse myocardial fibrosis without inflammatory infiltrate in a patient with myxedema, consistent with cardiomyopathy.[13] These reports show that the echocardiographic findings revert to normal after treatment with thyroid hormone.

***Therapeutic options in patients with cardiomyopathy secondary to hypothyroidism***

It has been shown that thyroid hormone replacement therapy can lead to a reversal of features of cardiomyopathy. However, if left untreated for a long time, irreversible myocardial damage can already occur.

**Subspecialty Forum**

*Endocrine service (Dr. Carlo Carreon):*

*To differentiate whether the patient had congenital or acquired hypothyroidism, we chose to do the anti-TPO because among the acquired causes of hypothyroidism, the most common would be the autoimmune diseases and anti-TPO has a sensitivity varying from 90-95% with specificity for Hashimoto's up to 100%. Results showed that the patient had a normal anti-TPO [**Ed.:** which is not consistent with acquired hypothyroidism due to an autoimmune cause]. However, several considerations that point against congenital hypothyroidism in this patient include the fact that the patient was normal at birth and that early in his life, the patient is not mentally retarded. However, literature search showed that mental retardation is really not absolute in congenital hypothyroidism as shown in various case reports. Also, some literature state that congenital hypothyroidism could actually manifest later in life. One theory is that the presence of a small remnant thyroid could compensate for the patient's thyroid requirements up to a point when the patient's metabolic needs increase (i.e., during the pubertal age) making this dysgenetic thyroid unable to meet the patient's metabolic requirements, and this is when the signs of hypothyroidism manifest.*

*In any case, there is no difference in terms of management of congenital or acquired hypothyroidism. Treatment of both would consist of thyroid hormone replacement in usual doses of 1.6-2.6 mcg/kg. In myxedema coma, doses usually start at 4mcg/kg, while in the elderly patients with heart problems, doses are lowered, usually at ~25mcg/day titrated up appropriately based on the patient's requirements.*

*CVS service (Dr. Ellaine Alajar / Dr. Dawn Nablo):*

- *In patients with hypothyroidism, there are some risk factors that actually predispose to development of coronary artery disease. One is dyslipidemia. Hypothyroidism is known to cause an increase in total cholesterol and lowered LDL levels because of the decreased LDL receptors in the liver. Hypothyroid patients are also noted to have arterial hypertension.*
- *This patient presented with hypotension that is why the service pushed for immediate coronary angiography to rule out a possible 3-vessel or left main coronary artery disease as the cause of the patient's dilated cardiomyopathy and hypotension.*
- *Considering this patient's condition, he would have succumbed to death to an invasive procedure such as CABG, however there are other measures which could be undertaken if it has actually been proven that the patient indeed had a coronary artery disease such as doing an intra-aortic balloon pump, which could actually improve the patient's preload and afterload however the cardiac output would probably not change significantly.*

*Endocrine service (Dr. Joselynna Quimpo):*

- *In an asymptomatic hypothyroid patient, we usually give the full dose (computed by weight) of levothyroxine right away the first time the patient comes to us for consult.*
- *However, in a patient presenting with signs of decompensation, we should be wary in increasing our doses of levothyroxine right away. In the guidelines for thyroid hormone replacement, some conditions should be taken into consideration when computing for our doses of thyroid hormone replacement such as congestive heart failure and arrhythmia. Excessive amounts of thyroid hormone can actually burden the heart more due to increased metabolic demands. The only time that we can actually give a high dose of levothyroxine in the initial phase is in myxedema coma because we would expect that the absorption phase of our oral levothyroxine would be poor.*
- *The dictum is to start slow, increase very slowly also.*

**Histopathologic Correlation**

As mentioned, postmortem examination was consistent with primary hypothyroidism with congestive heart failure from dilated cardiomyopathy. On external examination, there was note of short stature, coarse facial features, periorbital puffiness, thickened lips, macroglossia, and minimal facial hair. There was also loose, coarse skin, minimal body hair, and short stocky limbs. There was no note of an umbilical hernia, contrary to initial physical examination upon admission. The patient had well-developed external genitalia and bilaterally

descended testes. There was also a genu varum and bilateral non-pitting edema.

On internal examination, pertinent findings were that of dextroscoliosis, cardiomegaly with pericardial effusion amounting to 150 mL, and atherosclerosis of coronary, cerebral, and major arteries. There was no note of any intracardiac masses or thrombi. Microscopic examination showed fatty infiltration and interstitial edema of cardiac tissue, with myocardial cell hypertrophy and myxedematous degeneration of the mitral valve. Chronic congestive changes were observed in the hepatic and lung tissues, and the abdominal cavity contained about 220 mL of ascitic fluid. The thyroid gland was hypoplastic, weighing less than 2 grams (NV 30-70g), and no lingual thyroid was appreciated. On histopathologic examination, the thyroid showed no evidence of inflammation or fibrosis (Figures 4A and 4B). The pituitary gland was of average size, with no note of any masses.

Autoimmune thyroiditis causes a decrease in intrathyroidal iodine stores, an increased iodine turnover, and defective organification. Chronic inflammation of the gland causes progressive destruction of the functional tissue with widespread infiltration by lymphocytes and plasma cells with epithelial cell abnormalities. In time, dense fibrosis and atrophic thyroid follicles replace the initial lymphocytic hyperplasia and vacuoles.

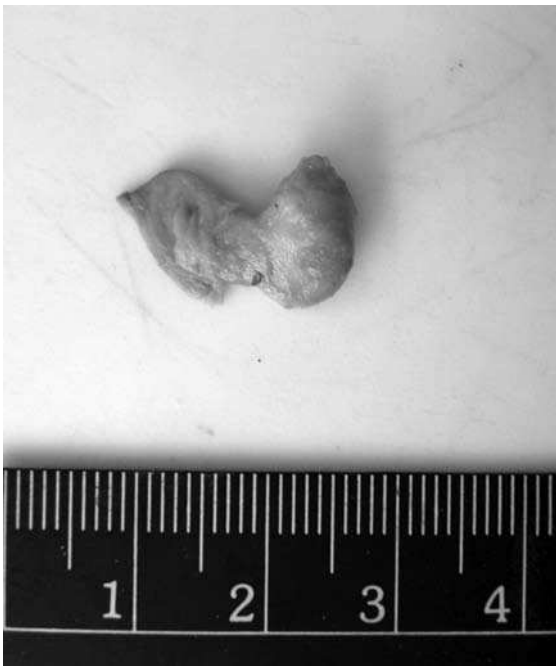


**Figure 4-A.** Post-mortem exam of patient revealed a hypoplastic thyroid.

**Final Anatomic Diagnosis:**

**I. MYXEDEMA**

A. Thyroid hypoplasia (<2 g)
B. Short stature (1.19 m)
   Coarse features, thickened lips, macroglossia, dry, loose, skin, bipedal non-pitting edema
C. Dilated cardiomyopathy in congestive heart failure
   1. Cardiomegaly (650 g).
      i. Concentric left ventricular hypertrophy and dilatation
      ii. Right ventricular hypertrophy and dilatation with fatty infiltration,
      iii. biatrial dilatation
   2. Myxomatous degeneration, mitral valve
   3. Pericardial effusion (150 cc)
   4. Chronic pulmonary congestion
      (480 g, R; 430 g, L) with edema and focal pulmonary hemorrhages
   5. Chronic passive congestion, liver (870g).
   6. Moderate ascites (220 cc).
D. Arteriosclerosis
   1. moderate to severe atherosclerosis
      - aorta, left and right coronary, common carotid, external and internal carotids, basilar, vertebral, intracerebral arteries
   2. Hyaline arteriolosclerosis.
      - renal arterioles
E. Calcific sclerosis, aortic valve

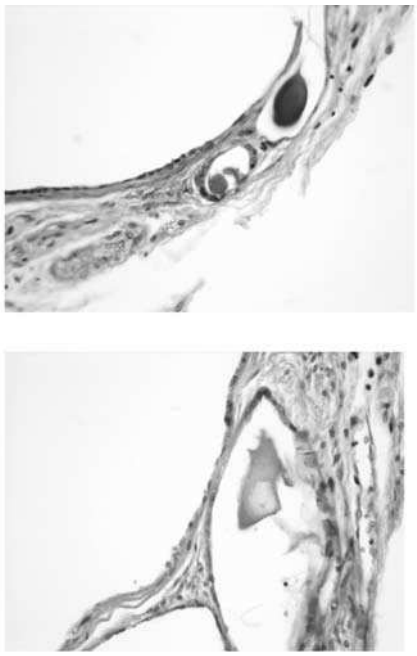

**Figure 4-B.** Microscopic exam showed presence of colloid and absence of inflammatory infiltrate

**II. BRONCHOPNEUMONIA**

**III. DYSTROPHIC CALCIFICATION WITH CHRONIC INTERSTITIAL NEPHRITIS**

**IV. ANGIODYSPLASIA, STOMACH, WITH FOCAL HEMORRHAGIC GASTRITIS**

**V. DEXTROSCOLIOSIS**

**CAUSE OF DEATH**

Congestive Heart Failure Secondary to Dilated Cardiomyopathy secondary to Primary Hypothyroidism

**Final Clinical Diagnosis:**

Congenital Hypothyroidism
Dilated Cardiomyopathy in Congestive Heart Failure in AHA Functional Class IV in sinus rhythm
Chronic passive congestion of liver
Dyslipidemia
Nosocomial pneumonia
Multiple electrolyte abnormalities

**CAUSE OF DEATH**

Decompensated Congestive Heart Failure Secondary to Dilated Cardiomyopathy secondary to Congenital Hypothyroidism

**Resolution and Conclusion**

These histopathologic findings were all consistent with primary hypothyroidism: myxedema, dilated cardiomyopathy in congestive heart failure, and arteriosclerosis. But it is well-known that primary hypothyroidism causes severe and permanent neurological damage (cretinism) early in life if not treated immediately. How then can this patient have reached adult age with functional mental capacity despite the absence of any hormone replacement? As discussed in this forum, this may have been possible because the patient had minimally-functioning thyroid tissue that sustained him in his early years. This thyroid tissue may be present along the embryologic origin of the thyroid from the base of the tongue and its descent route to its normal anatomic position at birth. This will account for sufficient quantities of hormone to prevent mental retardation but not enough to avert the clinical consequences of cardiomyopathy, dyslipidemia, and short stature.

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