

Severe Myocardial Ischemia following Hormone Replacement in Two Cases of Hypothyroidism with Normal Coronary Arteriogram

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Abstract. Two cases of hypothyroidism with cardiac attack (acute myocardial infarction, AMI) following thyroxine replacement were reported. Neither of these cases showed any major coronary artery disease. The first case was a 58-year-old male who was treated with L-thyroxine (initial dose 0.025 mg/day) for hypothyroidism due to Hashimoto's disease. The dose was increased up to 0.1 mg/day within 2 weeks. Acute myocardial infarction occurred 6 weeks after the replacement was started. Angiographical study showed no notable pathological change in major coronary arteries, but echocardiography demonstrated diffuse hypokinesis of the left ventricular wall. The second case was a 61-year-old female who suffered from Graves' disease and had been treated with thiamazole (2.5 mg/day) for 15 years. Later, she became hypothyroid and was treated with thyroxine. At first, 0.05 mg/day of L-thyroxine was given, and then the dose was increased up to 0.1 mg/day after the 7th week. Acute myocardial infarction occurred 3 weeks after the dose was increased. Angiographic study of the coronary arteries revealed no abnormality. Possible causes of AMI in thyroxine replacement were discussed in relation to vascular spasm and small vessel disease of the heart. Importance of echocardiographic study before hormone replacement therapy is stressed, particularly for middle/old-aged patients with long-term hypothyroidism.

Key words: Hypothyroidism, Thyroxine, Myocardial ischemia, Cardiomyopathy, Arteriography
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ADMINISTRATION of thyroid hormones may induce a cardiac attack even in cases with no history of anginal syndrome at the time thyroid replacement was started (angina pectoris or AMI) [1]. The mechanism of this phenomenon has been speculated to be by either a direct effect of the hormone on the heart [2] and/or by coronary vasospasm provoked by relative hyperthyroidism with possible underlying atheromatous coronary disease [3]. Physiologic effects of epinephrine and norepinephrine may be im-

portant in terms of an increase in the oxygen requirement, stroke volume and output of the heart. Practically, it may be rare to meet such cases particularly in subjects with normal coronary arteriogram, and only four such cases [4–7] have been reported in the world literatures at this time. In this communication, two cases are added to the record.

Case Reports

Case 1

A 58-year-old male suffered from proximal pain and sensory disturbance in distal parts of the limbs for the past 3 years. Edema was also noted in the

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lower limbs. He was admitted to our hospital in April, 1998 with chief complaint of myalgia in the limbs.

He used to have a smoking habit for 27 years (15–90 cigarettes/day), but had not smoked for the past 10 years. He drank no alcohol. Notable past history of diseases were: renal lithiasis at age 30 (familial renal lithiasis, father and two brothers), hypertension at age 52, colonic carcinoma treated by endoscopic mucosal resection at age 53.

A diagnosis of Hashimoto's disease with hypothy-

roidism was made based on physical (goiter, dry skin, non-pitting edema of the lower limbs, elongation of Achilles tendon reflex) and laboratory findings (Table 1). After oral administration of L-thyroxine (thyroxine) (0.025 mg/day) from May 6, all symptoms including myalgia began to subside. Thyroxine dose was increased to 0.05 mg/day on day 13, and to 0.1 mg/day on day 18. He was discharged from the hospital on May 18, 19 days after admission.

About a month after discharge, he had a feeling of

Table 1. Hematologic, blood, chemical, and thyroid function laboratory values (Case 1)

| VARIABLE | on first admission | on second admission |
|---|--------------------|---------------------|
| Hemoglobin (g/dl) | 11.1 | 10.4 |
| Hematocrit (%) | 32.6 | 31.2 |
| Platelet count (per μ l) | 15.9×10^4 | 25.5×10^4 |
| White cell count (per μ l) | 4760 | 9760 |
| Differential count (%) | | |
| Neutrophils | 56.0 | 75.0 |
| Lymphocytes | 31.9 | 16.2 |
| Monocytes | 4.4 | 6.6 |
| Eosinophils | 7.1 | 1.9 |
| Basophils | 0.6 | 0.3 |
| Total protein (g/dl) | 8.6 | 7.6 |
| Urea nitrogen (mg/dl) | 27.5 | 27.1 |
| Creatinine (mg/dl) | 2.6 | 1.7 |
| Sodium (mEq/liter) | 134 | 141 |
| Potassium (mEq/liter) | 3.6 | 4.0 |
| Chloride (mEq/liter) | 91 | 103 |
| Calcium (mg/dl) | 10.0 | 9.6 |
| Lactate dehydrogenase (IU/liter) | 581 | 615 |
| Aspartate aminotransferase (U/liter) | 91 | 84 |
| Alanine aminotransferase (U/liter) | 55 | 14 |
| Total-bilirubin (mg/dl) | | 0.6 |
| Total cholesterol (mg/dl) | 376 | 136 |
| Creatine phosphokinase (mg/dl) | 2953 | 561 |
| -brain band (%) | 0 | 0 |
| -myocardial band (%) | 2 | 9 |
| -muscle band (%) | 98 | 91 |
| Myosin light chain (ng/ml) (<2.5) | | 2.6 |
| Troponin-T (ng/ml) (<0.25) | | 7.52 |
| C-reactive protein (mg/dl) | 0.2 | 0.6 |
| Thyroid stimulating hormone (μ U/ml) (0.4–3.7) | 220.8 | 27.7 |
| Free-thyroxine (ng/dl) (0.8–1.7) | 0.2 | 1.4 |
| Free-triiodothyronine (pg/ml) (2.2–4.1) | 1.1 | 2.8 |
| Thyroglobulin hemagglutination (titer) (<100) | 409600 | |
| Microsome hemagglutination (titer) (<100) | 409600 | |
| Thyroglobulin antibody (U/ml) (<0.3) | >100 | |

compression in the anterior chest while driving a car. The symptom worsened and developed to anterior chest pain by exercise. He was re-admitted on June 18, 1998. On physical examination: afebrile, blood pressure 190/100 mmHg, enlarged elastic thyroid, normal cardiac sounds with no murmur, no edema on the limbs.

Laboratory data (Table 1) showed that thyroid hormones were within normal range except for elevated TSH. Creatine-kinase level was elevated. Electrocardiogram (ECG) (Fig. 1) showed slightly elevated ST in V1 to V3, depressed ST in II, III, aVF, V5 and V6, compared to the ECG obtained before the replacement therapy, on April 28. Later ECG

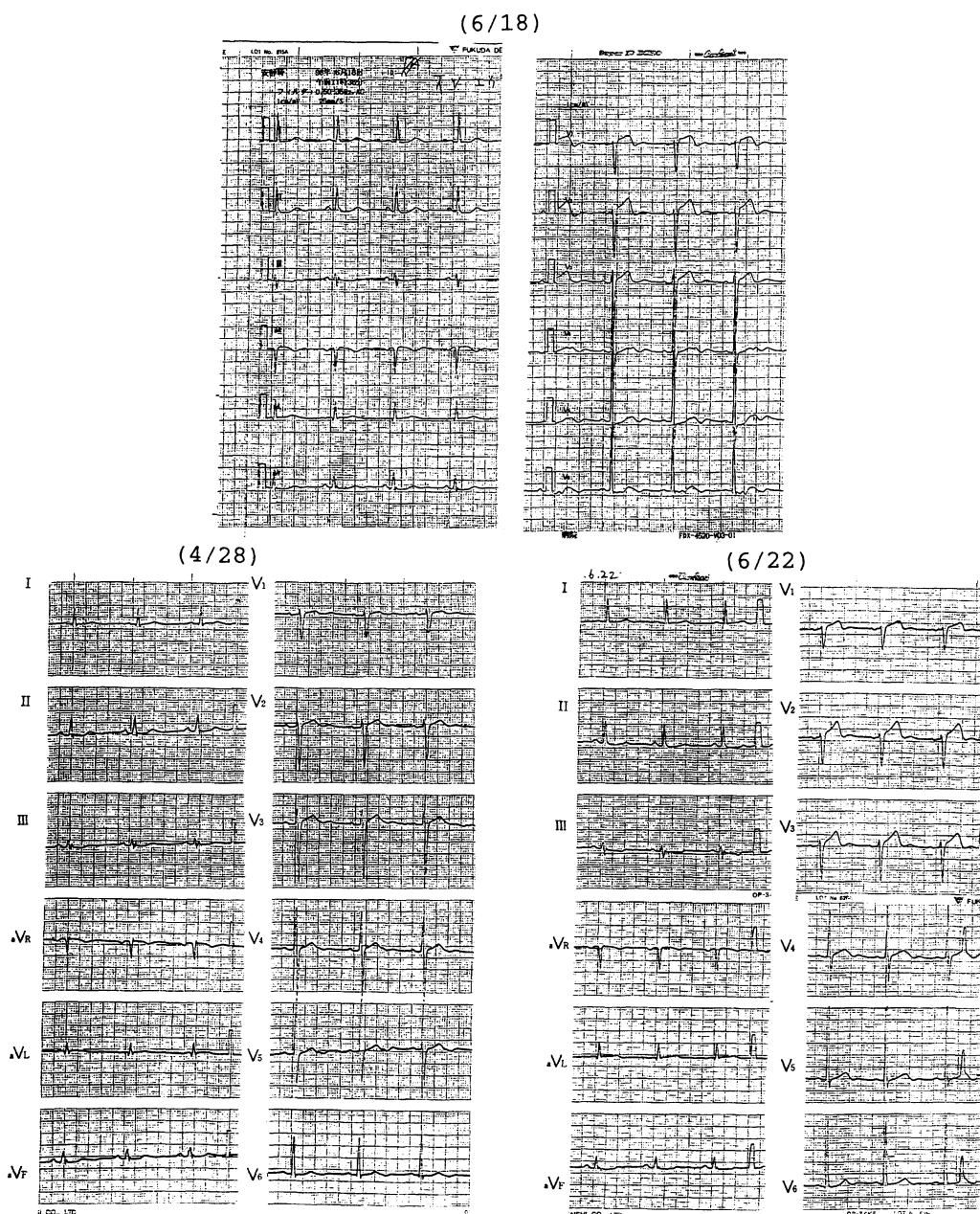


Fig. 1. ECG (Case 1). ECG obtained on June 18th at the time of chest pain, showing slight ST elevation in V1–V3, ST depression in II, III, aVF, V5 and V6 compared to the ECG on Apr. 28th. ECG obtained later on (June 22nd) shows poor R wave progression, recovering ST in V5 and V6.

(6/22) showed poor R wave progression in V3, recovering ST in V5 and V6, that indicated that myocardial ischemia had occurred at a subendocardial site. Thickening and hypokinesis of the rest of the left ventricular wall were shown on echocardiography (Fig. 2). From these data, AMI or acute myocarditis was suspected.

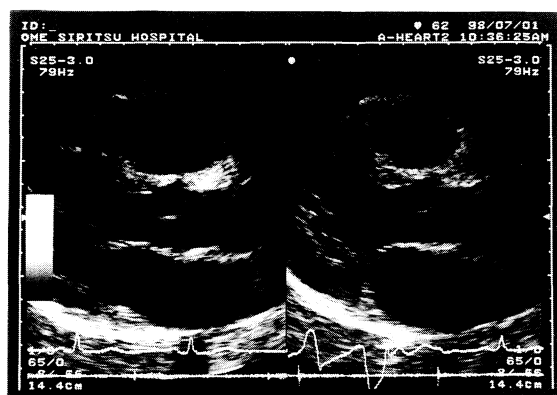
After admission, the administration of thyroxine was discontinued and isosorbide dinitrate was given intravenously. He was kept at bed-rest under observation. By these treatments, his creatine-kinase level fell rapidly to a normal range, and the chest pain disappeared 12 hours after admission (the feeling of compression improved on the 9th hospital day). Thyroxine administration (0.025 mg/every other day) was resumed. Arteriographic study (Fig. 3) performed on the 30th hospital day revealed a left dominant coronary system with 50% stenosis in posterior descending branch and non-remarkable others. Left

cineangiogram (Fig. 4) showed diffuse hypokinesis of the left ventricle with considerably well maintained angiographic ejection fraction (0.57), and no focal asynergetic segments. He was discharged on the 41st hospital day.

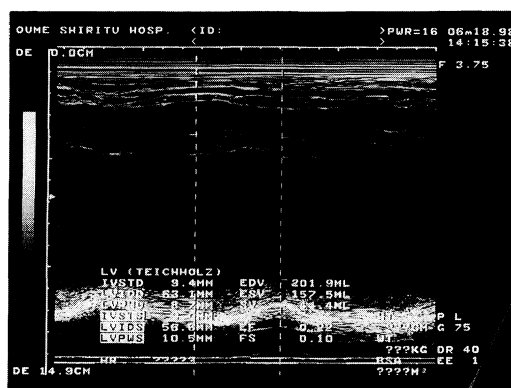
Thyroxine dose was gradually increased up to 0.1 mg/day. His course thereafter went well and no anginal attack has occurred up to now. The clinical course of this case is shown (Fig. 5).

Case 2

A 61-year old woman was admitted with a complaint of chest pain in March, 1996. She had a history of Graves' disease since age 45 and had been treated with thiamazole. She reached euthyroidism at age 52, and later fell into hypothyroidism in spite of the administration of a small dose of thiamazole (5 mg/every other day). Thiamazole administration



B mode



M mode

Fig. 2. Echocardiogram (Case 1). Septal thickening and hypokinesis of the left ventricular wall is shown.

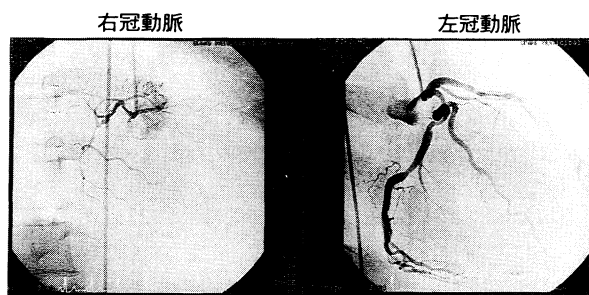


Fig. 3. Coronary arteriogram (Case 1). A left dominant coronary system with 50% stenosis in posterior descending branch is shown.

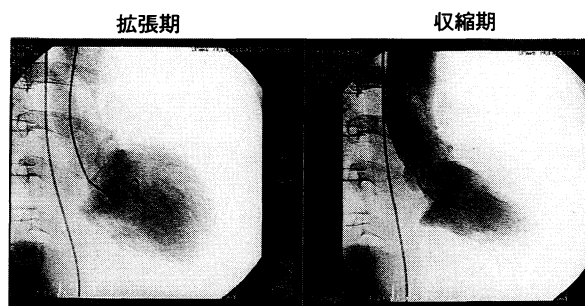


Fig. 4. Left cineangiogram (Case 1). Slight diffuse hypokinesis of the left ventricle with an ejection fraction of 0.57, and no focal asynergy is seen.

| Date | (4/28) | (5/11) | (5/18) | (6/8) | (6/18) | (6/19) | (6/22) | (6/29) | (7/13) | (8/18) |
|--------------------|------------|------------|------------|-------|--------------|--------|--------|--------|-----------------------|--------|
| CPK (U/l) | 2953 | 1763 | 745 | 95 | 561 | 298 | 54 | 39 | 54 | |
| TSH (μ U/ml) | 220.8 | | 189.4 | 27.7 | | | 28.6 | | 153.7 | 165.6 |
| FT4 (ng/ml) | 0.2 | | 0.5 | 1.4 | | | 0.8 | | 0.4 | 0.2 |
| FT3 (pg/ml) | 1.1 | | 1.4 | 2.8 | | | 2.1 | | 1.4 | 1.5 |
| Tchol (mg/dl) | 376 | 316 | 300 | 138 | 136 | | | 155 | 197 | 294 |
| | \uparrow | \uparrow | \uparrow | | \uparrow | | | | \uparrow | |
| | (5/6) | (5/13) | (5/19) | | (6/18) | | | | (7/10) | |
| l-T4 dose (mg/day) | 0.025 | 0.05 | 0.1 | | discontinued | | | | 0.025 every other day | |
| chest pain | | | | | | | | | | |

Fig. 5. Clinical course of Case 1. High level of CPK at the time of diagnosis of hypothyroidism falls rapidly as the data reaches euthyroid level. Note that the level of total cholesterol has fallen to normal range in less than 6 weeks. CPK elevates again at the time of chest pain occurrence, and l-T4 is discontinued. On July 13th, low dose of l-T4 administration is resumed, the dose escalation being done gradually.

was discontinued at age 61 because laboratory data showed high TSH level, and thyroxine administration (0.05 mg/day) was started in December, 1994. Thyroxine dose was increased to 0.1 mg/day from February 7, 1996. On March 1, she was awakened by pain in the retrosternal region and was admitted 18 hours after onset. Physical examination on admission revealed no abnormal findings except for a goiter. ECG (Fig. 6) showed an ST elevation in V5 and V6, negative T in II, III, aVF, V5 and V6, small q in III. High creatine kinase level was noted (Table 2). Echocardiography showed mild hypokinesis from the apex to the inferior wall of the left ventricle. From these data, a clinical diagnosis of AMI was made. Thyroxine administration was discontinued. Coronary angiography (Fig. 7) on the 23rd hospital day showed normal arteriogram. Cine-angiogram (Fig. 8) showed a reduced motion of the left apex wall. She was discharged on the 34th hospital day.

After discharge, thyroxine administration (0.025 mg/day) was resumed, and neither chest pain nor oppressive feeling of the chest have appeared. Later, her hyperthyroidism relapsed and thiamazole administration was started from June, 1998.

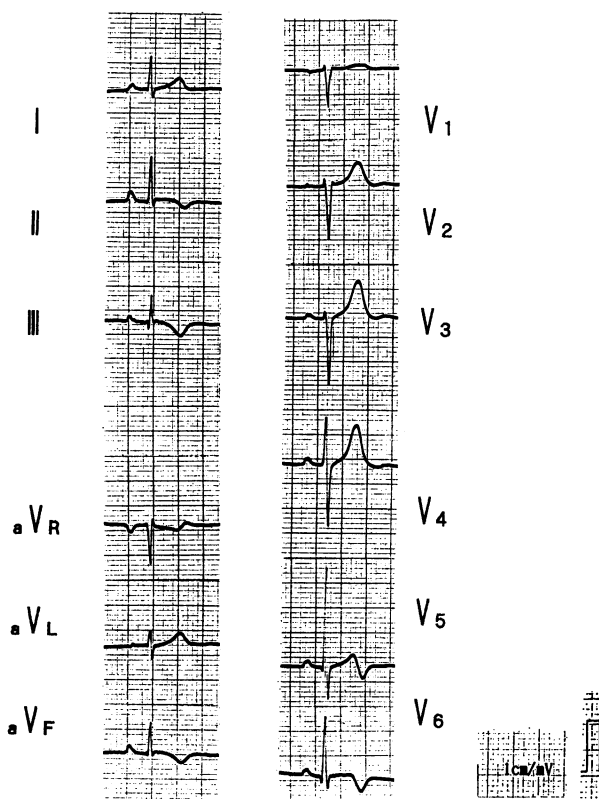


Fig. 6. Electrocardiogram (Case 2). Negative T in II, III, aVF, V5 and V6 is detected.

Table 2. Hematologic, blood, chemical, and thyroid function laboratory values (Case 2)

| VARIABLE | before l-T4 replacement | after l-T4 replacement |
|---|-------------------------|------------------------|
| Hemoglobin (g/dl) | 13.1 | 14.2 |
| Hematocrit (%) | 40.1 | 44.1 |
| Platelet count (per μ l) | 14.2×10^4 | 15.8×10^4 |
| White cell count (per μ l) | 4350 | 6590 |
| Differential count (%) | | |
| Neutrophils | 66.3 | 80.6 |
| Lymphocytes | 29.9 | 26.8 |
| Monocytes | 1.6 | 2.1 |
| Eosinophils | 0.9 | 0.2 |
| Basophils | 0.9 | 0.3 |
| Total protein (g/dl) | 6.6 | 7.5 |
| Urea nitrogen (mg/dl) | 15.7 | 11.1 |
| Creatinine (mg/dl) | 0.7 | 0.7 |
| Sodium (mEq/liter) | 144.4 | 141 |
| Potassium (mEq/liter) | 3.9 | 3.6 |
| Chloride (mEq/liter) | 103.7 | 100 |
| Calcium (mg/dl) | 8.7 | 8.3 |
| Lactate dehydrogenase (IU/liter) | 437 | 512 |
| Aspartate aminotransferase (U/liter) | 19 | 55 |
| Alanine aminotransferase (U/liter) | 12 | 12 |
| Total-bilirubin (mg/dl) | 0.9 | 1.3 |
| Total cholesterol (mg/dl) | 269 | 216 |
| Creatine phosphokinase (mg/dl) | 310 | 653 |
| -brain band (%) | | 0 |
| -myocardial band (%) | | 6 |
| -muscle band (%) | | 94 |
| Myosin light chain (ng/ml) (<2.5) | | 3.0 |
| Thyroid stimulating hormone (μ U/ml) (0.4–3.7) | 114.7 | 5.3 |
| Free-thyroxine (ng/dl) (0.8–1.7) | 0.4 | 1.7 |
| Triiodothyronine (pg/ml) (2.2–4.1) | 106 | |
| Thyroglobulin hemagglutination (titer) (<100) | <100 | <100 |
| Microsome hemagglutination (titer) (<100) | 100 | 100 |
| Thyroglobulin (RIA) (U/ml) (<30) | 43 | 35 |
| TSH receptor antibody | (+) | |
| TSH binding inhibition (%) | 94.3 | |

Discussion

Three mechanisms have been proposed for acute myocardial ischemia occurring during thyroid replacement therapy in cases with normal coronary arteriograms: 1. transient occlusion of major coronary arteries, 2. small vessel disease, and 3. an increase in myocardial oxygen demand.

Transient coronary occlusion may be caused by either thromboembolism with subsequent thrombolysis or vasospasm. Thromboembolism is associated

most frequently with left atrial overload and prior atrial fibrillation. These changes were not seen in our cases. Vasospasm, a cause of reversible ischemia and/or myocardial infarction, in thyrotoxicosis is common [8–12]. It is likely that thyroxine increases the activity of a β -adrenergic receptor of coronaries, and that coronary spasm may be induced by an excess level of free catecholamine. Since neither intravenous nor intracoronary injection of ergonovine maleate was performed in either case, it is difficult to estimate the occurrence of coronary spasm in our

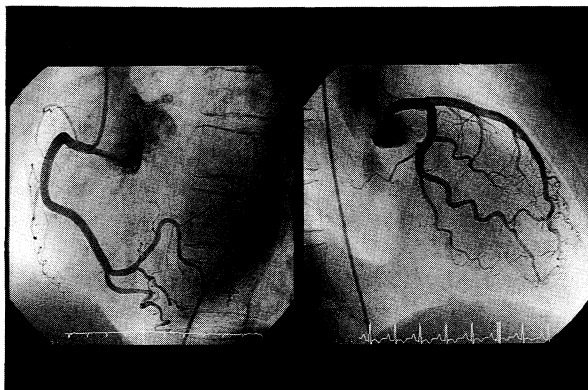


Fig. 7. Coronary arteriogram (Case 2). Normal coronary system.

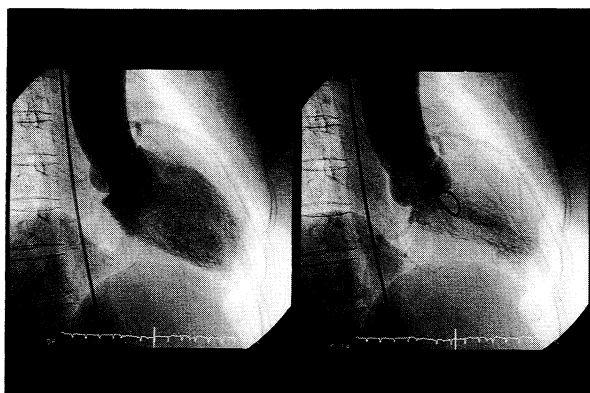


Fig. 8. Left cineangiogram (Case 2). A reduced motion of the apex wall is shown.

cases.

Small vessel disease most commonly occurs in cases with diabetes mellitus and primary cardiomyopathy. Echocardiography on myxedema shows a result similar to that of idiopathic hypertrophic sub-

aortic stenosis [13]. Asymmetric septal hypertrophy with or without reduction of the left ventricular out-flow dimension and systolic anterior motion of mitral valve leaflets are seen in most cases of untreated myxedema. It has been also reported that myocardial hypertrophy in hypothyroidism improved by thyroid hormone replacement [13, 14]. This suggests that long-term hypothyroidism may lead to reversible cardiomyopathy. Ventricular septal hypertrophy with severe hypokinesis noted in Case 1 suggests that cardiomyopathy and small vessel disease were already present in Case 1. No similar abnormality was noted in Case 2.

Myocardial ischemia occurs due to an excess imbalance of oxygen supply/demand in the myocardium. Regardless of the site of the disturbance, a critical imbalance may result in angina pectoris or myocardial infarction. We assume that cardiomyopathy existed in Case 1 due to long term hypothyroidism, and that the rapid increase of thyroxine induced by hormone replacement resulted in relative hyperthyroidism and induced AMI in the cardiomyopathic heart. The mechanism of AMI noted in Case 2 is difficult to explain. Hypothyroidism in this case was relatively short and not likely to induce cardiomyopathy. Increasing the dose of thyroxine was done gradually and carefully using a month period. We speculated that the attack of this case was rather accidental.

Reviewing the clinical records of our present cases, we concluded that the starting dose and dose-increase of thyroxine in the replacement therapy must be made carefully, particularly in middle/old-aged cases with long-term hypothyroidism. When cardiac catheterization is not feasible, evaluation of cardiac condition by echocardiography before replacement therapy is highly recommended.

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