

Successful treatment of myxedema coma with a combination of levothyroxine and liothyronine

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Abstract. Myxedema coma is a rare endocrine emergency resulting from the decompensation of severe hypothyroidism, which is associated with a high mortality rate. It is characterized by the deterioration of mental status, hypothermia, hypotension, hyponatremia, and hypoventilation. Early disease diagnosis and advancements in intensive supportive care have reduced the mortality rate. Besides intensive supportive care, appropriate management of the underlying thyroid hormone deficiency is essential. However, as the disease is rare and unrecognized, evidence-based treatment of myxedema has not yet been established in many countries. An 84-year-old Japanese man with a history of Hashimoto's thyroiditis was referred to our hospital. On arrival, conscious disturbance, hypothermia, hypotension, and hypoventilation were observed. He had discontinued thyroid hormone replacement therapy for a year. He was diagnosed with myxedema coma. Immediately, he received intensive supportive care and a combination therapy of 200 µg levothyroxine and 50 µg liothyronine until the fifth hospital day. Subsequently, monotherapy with levothyroxine was continued at a dose of 150 µg daily. The thyroid hormone level reached the normal range a few days later, and cardiovascular disease did not develop during hospitalization. This case demonstrated the efficacy of the combination of levothyroxine and liothyronine in treating myxedema coma.

Key words: Levothyroxine, Liothyronine, Myxedema coma

MYXEDEMA COMA is a medical emergency, and the mortality associated with this condition may be as high as 25%–60%, even with the best possible treatment [1-4]. Treatment of myxedema coma requires multiple treatments such as respiratory care, circulation management, adrenocortical hormone administration, and thyroid hormone replacement. Among these treatments, thyroid hormone replacement therapy is particularly important. However, in many countries, evidence-based treatment of myxedema has not yet been established. In many cases, myxedema coma has been treated based on expert opinion and previous case reports [5-8]. There are some challenges associated with thyroid hormone replacement, and the optimal dosage of the hormone and the administration route need to be ascertained. Levothyroxine (LT4) is intravenously administered in many countries, and is regarded as the standard therapy for myxedema coma [7]. In Japan, thyroid hormone replacement is performed using the nasogastric tube in patients with myxedema coma. Furthermore, whether myxedema

coma should be treated with LT4 alone or with both LT4 and liothyronine (LT3) remains controversial [5-8]. We herein report a case of myxedema coma, which was treated with a combination of LT4 and LT3.

Case Report

An 84-year-old Japanese man was referred to the emergency department at our hospital owing to disturbance of consciousness in April 2017. He was diagnosed with Hashimoto's thyroiditis in 2005 and oral LT4 medication was initiated. He had no medication other than LT4. He had discontinued his medication without consulting a doctor a few times, and he had discontinued thyroid hormone replacement therapy for a year. He was self-reliant in day-to-day life; however, his activities had gradually declined over the past two months. Finally, he could not take ingest food several days before admission. On arrival, his Glasgow Coma Scale (GCS) score was 3/15 (E1V1M1). His height was 160.0 cm, weight was 55.0 kg, and body mass index was 21.5 kg/m². Physical examination showed a pulse rate of 50 beats/min, a rectal temperature of 31.0°C, and respiratory rate of 18 cycles/min; however, blood pressure and oxygen saturation were not measurable. We observed prominent edema on the face, neck, trunk, and limbs. Laboratory findings

Submitted Nov. 14, 2018; Accepted Feb. 7, 2019 as EJ18-0469
Released online in J-STAGE as advance publication Mar. 8, 2019
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showed hepatic dysfunction, renal failure, elevated creatinine kinase level, low blood glucose level, and severe hypothyroidism; moreover, arterial blood gas analysis revealed type II respiratory failure (Table 1). Chest X-ray showed right pleural effusion (Fig. 1A). Computed tomography of the chest and abdomen showed bilateral pleural effusion, ascites, and pericardial effusion (Fig. 1B, 1C). An echocardiogram revealed diffuse hypokinesis of the left ventricle with pericardial effusion (Fig. 1D). An electrocardiogram showed sinus arrest, supplemental rhythm, and low voltage in the limb leads (Fig. 1E). Following the guidelines of the Japan Thyroid Association, clinical findings including hypothyroidism, consciousness disturbance, hypothermia, hypotension and hypoventilation were used as diagnostic criteria for myxedema coma, and myxedema coma was indicated.

He immediately received general emergency treatment. Noradrenaline was administered to maintain blood

pressure, and glucose was injected to increase the blood glucose level. He was placed under noninvasive positive pressure ventilation (NPPV) due to hypoventilation. Although his blood glucose was restored to the normal level, his consciousness had not improved. Considering the possibility of secondary adrenal insufficiency, adrenocortical hormone was administered through an intravenous infusion of 100 mg hydrocortisone every 8 h. Thyroid hormone replacement therapy was subsequently performed at an initial dose of 100 µg LT4 and 25 µg LT3 every 12 h through the nasogastric tube. On the second hospital day, free-triiodothyronine (fT3) was determined to be within normal limits (1.12 pg/mL). His GCS score was 6/15 (E1V1M4), and he gradually started to regain consciousness. It was not until the third hospital day that free-thyroxine (fT4) concentration could be measured (0.49 ng/dL). Since his blood pressure was gradually increasing, the doses of noradrenaline were

Table 1 Laboratory data on admission

[Complete blood count]			[Blood chemistry analysis]		
WBC	2,300/µL	(4,000–9,000)	TP	5.7 g/dL	(6.7–8.3)
Differential			ALB	2.6 g/dL	(4.0–5.0)
Seg 80.3%, Lym 11.4%, Mo 8.3%, Eo 0.0%, Ba 0.0%			BUN	43 mg/dL	(8–22)
RBC	$378 \times 10^4/\mu\text{L}$	(430–574)	Creatinine	1.47 mg/dL	(0.6–1.0)
HGB	11.9 g/dL	(13.2–16.4)	UA	8.3 mg/dL	(3.6–7.0)
PLT	$53 \times 10^4/\mu\text{L}$	(150–350)	Na	146 mEq/L	(138–146)
[Arterial blood gas analysis (O ₂ 10 L)]			K	3.3 mEq/L	(3.6–4.9)
pH	7.160	(7.35–7.45)	Cl	109 mEq/L	(99–109)
pCO ₂	90.2 Torr	(35–45)	Ca	8 mg/dL	(8.8–10.2)
pO ₂	88.8 Torr	(75–100)	CPK	2,383 IU/L	(50–200)
HCO ₃	29.8 mmol/L	(20–26)	AST	187 IU/L	(7–38)
BE	0.3 mmol/L	(–3–+3)	ALT	74 IU/L	(4–34)
[Endocrine and immunology]			T-bil	0.7 mg/dL	(0.2–1.2)
TSH (CLIA)	>100 µIU/mL	(0.35–4.94)	CRP	1.81 mg/dL	(0–0.14)
fT3 (CLIA)	<1.00 pg/mL	(1.71–3.71)	PG	21 mg/dL	(70–109)
fT4 (CLIA)	<0.40 ng/dL	(0.70–1.48)	PT	14.8 sec	(10.0–13.0)
TG (ECLIA)	3.55 ng/mL	(<33.7)	APTT	37.8 sec	(24.0–37.0)
Anti TG Ab (ECLIA)	>4,000 IU/mL	(<28)	Fibrinogen	334 mg/mL	(200–500)
Anti TPO Ab (ECLIA)	>600 IU/mL	(<16)	FDP	7.1 µg/mL	(<5.0)
			D-dimer	3.24 µg/mL	(<1.00)
			AT III	70%	(80–130)

Parentheses : Reference Values

WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; TSH, thyrotropin; fT3, free-triiodothyronine; fT4, free-thyroxine; TG, thyroglobulin; Anti TG Ab, anti-thyroglobulin antibody; Anti TPO Ab, anti-thyroid peroxidase antibody; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; CPK, creatinine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin; CRP, C-reactive protein; PG, plasma glucose; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrin degradation product; AT III, antithrombin III.

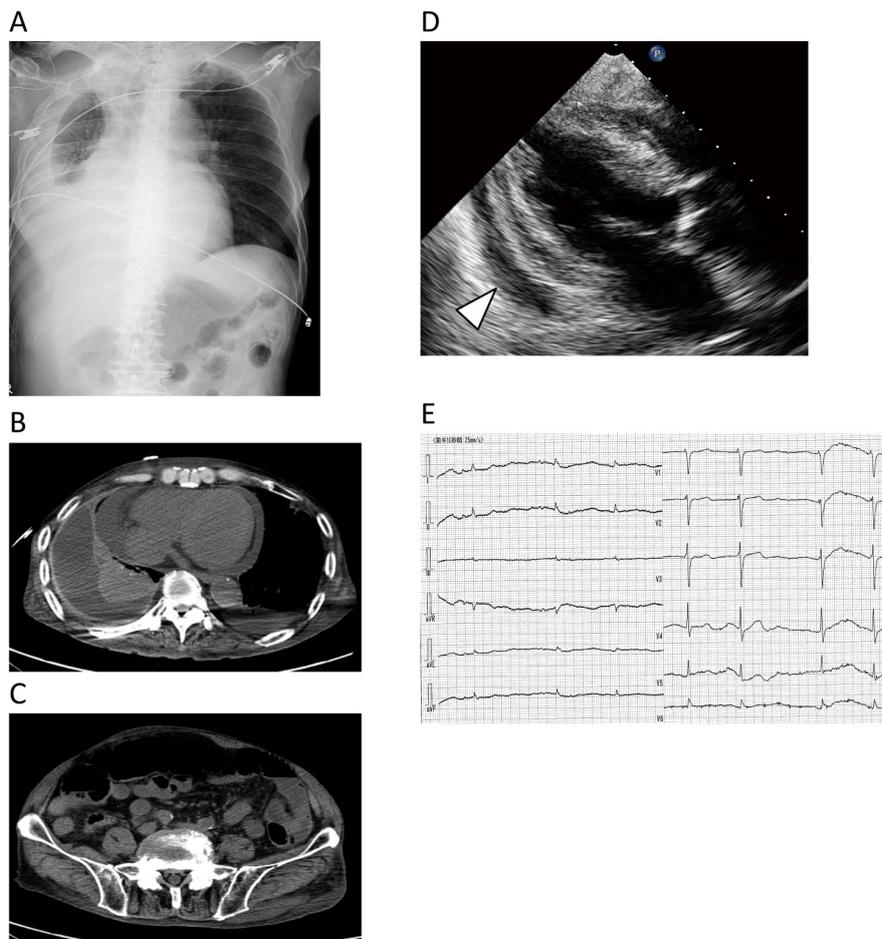


Fig. 1 Chest X ray, computed tomography of the chest and abdomen, echocardiogram, and electrocardiogram. (A) Chest X ray on admission showed right pleural effusion. (B and C) Computed tomography of the chest (B) and abdomen (C) on admission showed bilateral pleural effusion, ascites and pericardial effusion. (D) Echocardiogram on the third hospital day revealed pericardial effusion (arrow head). (E) Electrocardiogram on admission revealed sinus arrest, supplemental rhythm and low voltage in the limb leads.

reduced. On the fourth hospital day, his fT3 level was restored to the normal value (1.88 pg/mL). He received a combination therapy of LT3 and LT4 until the fifth hospital day; subsequently, monotherapy with LT4 was continued at a dose of 150 µg daily. The serum levels of fT3, fT4, and thyroid-stimulating hormone were approximately maintained within the normal range, and his physical condition including conscious state, respiratory state, circulation, and edema gradually began to improve. NPPV was withdrawn on the seventh hospital day. On the eighth hospital day, his GCS score was 13/15 (E4V4M5), and we discontinued the administration of noradrenaline and hydrocortisone. There were no signs of adrenal insufficiency such as low blood glucose level and low blood pressure even after discontinuation of noradrenaline and hydrocortisone. The thyroid hormone level reached the normal range a few days later, and cardiovascular disease did not develop during hospitalization. He was moved to another hospital for rehabilitation

on the forty-fifth hospital day. His clinical course is shown in Fig. 2.

Discussion

Myxedema coma is typically a sequela of chronic thyroid hormone deficiency and is characterized by the deterioration of mental status, hypothermia, hypotension, hyponatremia, and hypoventilation. It is one of the most urgent and lethal endocrine conditions. In the past, the overall mortality rate for myxedema was 60%–70% [2]. Early disease diagnosis and advancements in intensive supportive care have reduced the mortality rate to 20%–50% [9]. Recently, a study of the national database in Japan revealed that the overall in-hospital mortality rate of myxedema coma was 29.5% [10]. Past history of hypothyroidism can be a potential clue for the diagnosis of myxedema coma. However, a previous study had reported that 39% of patients with myxedema coma had

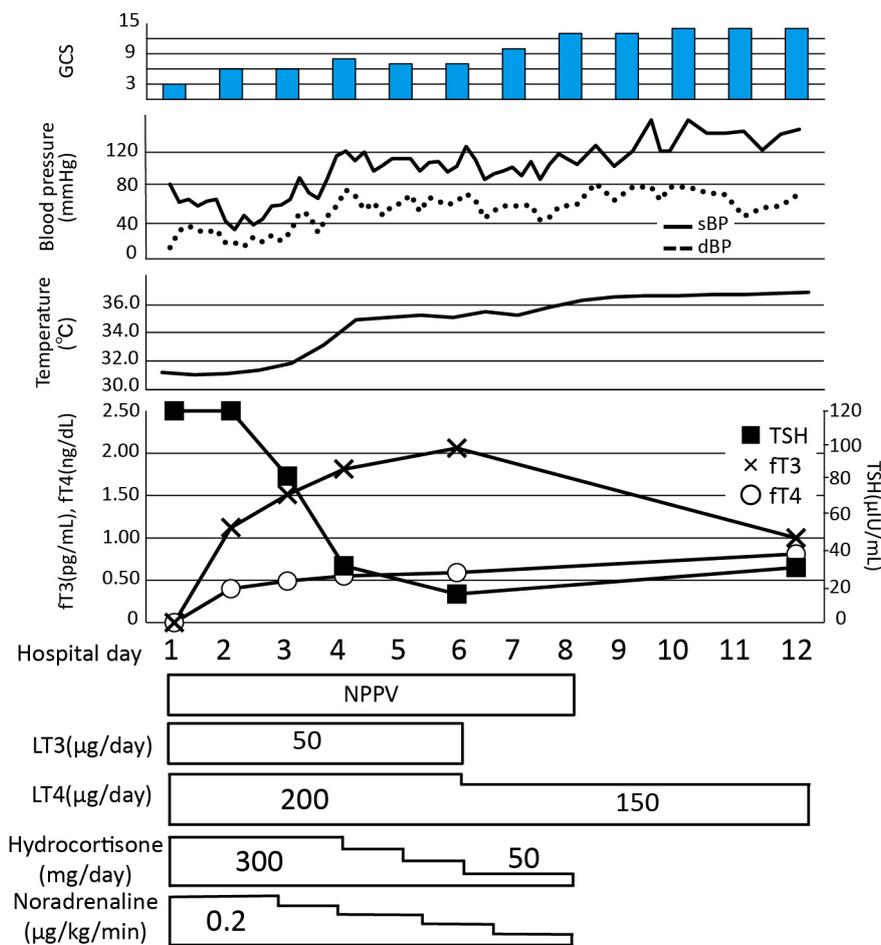


Fig. 2 Clinical course after admission. Temperature was measured in the rectum on the first hospital day, and subsequently in the axilla. sBP, systolic blood pressure; dBP, diastolic blood pressure

no history of hypothyroidism [11]. In the present case, the past medical history of Hashimoto's thyroiditis was a clue for early diagnosis and treatment.

There are no globally validated diagnostic criteria for myxedema coma owing to its rarity and sudden onset. In clinical practice, myxedema coma is often diagnosed based on symptoms and clinical examination, without waiting for laboratory results [12]. Currently, one study from the United States has reported a diagnostic scoring system for myxedema coma that is useful for early recognition of the illness [13]. In Japan, an original diagnostic criterion for myxedema coma was proposed by the Japan Thyroid Association but has not been validated. Using this criterion, the patient in this case was diagnosed with myxedema coma.

Besides intensive supportive care, appropriate management of the underlying thyroid hormone deficiency is essential. However, as the disease is rare and unrecognized, any recommendations for the treatment of myxedema, such as intravenously administration of LT4 and intravenous or nasogastric administration of high- or

low-dose LT3, have merely been based on expert opinion and previous case reports [5-8]. LT4 is intravenously administered in many countries, which is regarded as the standard therapy for myxedema coma [7]. It should be considered that if the thyroid hormone deficiency is profound enough to result in laryngeal edema, bowel edema is also likely to be present, and the intravenous route should be adopted to ensure adequate delivery of the replacing hormone [14]. Conversely, Dotta *et al.* [4] reported that the outcome of myxedema coma was not influenced by the route of LT4 administration. Intravenous infusion of thyroid hormones is not practiced in Japan, and their replacement is performed orally through a nasogastric tube. In this case, thyroid hormone replacement was performed by enteral administration, and a gradual increase in the plasma T3 and T4 levels was observed.

Cardiovascular diseases were the most frequent comorbidity observed in patients with myxedema coma at the time of admission. It has been reported that rapid increase in serum thyroid hormone concentrations in

long-standing hypothyroidism is associated with high risks of induction of myocardial infarction or arrhythmia [15, 16]. Analysis of the national inpatient database in Japan [10] revealed that no patients were identified to have newly diagnosed acute myocardial infarction or lethal arrhythmia after thyroid hormone replacement, suggesting that the gradual increase in plasma T4 and T3 levels by enteral administration of thyroid hormones resulted in slower cardiovascular responses compared with intravenous administration [17].

The issue of whether myxedema coma should be treated by administering LT4 alone or with a combination of LT4 and LT3 remains controversial [5-8]. Ono *et al.* [10] reported that patients who received LT4 combined with LT3 had a lower mortality rate than those who received LT4 alone, but this difference was not statistically significant. Treatment with LT4 has a slow onset of action with relatively few adverse events, whereas T3 is an active hormone in the body with immediate action because its affinity for the nuclear receptor is 10- to 20-fold higher than that of T4, and also because T3 reaches a peak level in 2–4 h after administration [18]. Beneficial effects of this combined treatment on neuropsychiatric symptoms are expected because T3 can cross the blood–brain barrier [19]. In healthy subjects, about 20% of the circulating T3 is secreted by the thyroid gland, while the majority of T3 production is based on conversion of T4 to T3. Conversely, peripheral conversion of T4 to T3 is decreased and reverse T3 is increased in patients with severe chronic illness [20]. These findings therefore suggest that the potential effects of combination treatment with LT3 and LT4 should be more beneficial than LT4 monotherapy to improve symptoms and to reverse the

biochemical abnormalities in patients with myxedema coma.

Yamamoto *et al.* [1] reported that doses of LT4 >500 µg per day or of LT3 >75 µg per day were associated with high mortality. The recommended initial intravenous dose of LT4 varies from 100 to 500 µg followed by daily maintenance of 50 to 100 µg until sensorium improves. The optimal dose of LT3 has rarely been reported. A previous report indicated that higher doses of LT3 (≥ 75 µg/day) were associated with fatal outcomes [1]. Particularly in older patients, thyroid hormone replacement therapy seems to be safer in lower doses than those conventionally recommended [1]. McCulloch *et al.* [21] reported on the efficacy of a low dose of oral LT3 (2.5 µg/day) in myxedema coma. In this case, we administered LT3 at a dose of 50 µg per day.

In summary, we herein reported a case of myxedema coma with a history of Hashimoto's thyroiditis and discussed the clinical course of the patient in detail. Our patient was successfully treated with a combination of LT3 and LT4, thereby revealing the efficacy of a combination of enteral LT4 and LT3 in the treatment of myxedema coma.

Acknowledgment

The authors are grateful to Dr. Hiroshi Yoshimura (Ito hospital, Tokyo, Japan) for the helpful discussion and suggestions.

This study was funded by Japanese Red Cross, Nagoya 1st. Hospital Research Grant NFRCH19-0004.

The authors state that they have no Conflict of interest (COI).

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