A case of fatal myxedema coma with electrocardiogram Osborne J-wave in a patient initially diagnosed with hypothyroidism

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Abstract. Myxedema coma is a life-threatening endocrine emergency with a high mortality rate resulting from severe insufficiency of thyroid hormones. Intravenous levothyroxine replacement is considered the standard therapy for myxedema coma in many countries. In Japan, however, although there are diagnostic criteria highly suggestive or diagnostic for myxedema coma, no management strategy has been established, despite the availability of levothyroxine. Here we report a 75-year-old man with a history of Alzheimer’s disease and schizophrenia who developed somnolence and generalized edema. Except for a pulse rate of 60 bpm, his vital signs and blood oxygen level were stable. Thyroid studies showed an elevated serum thyrotropin level of 219.2 μU/mL and a decreased serum free-thyroxine level of 0.15 ng/dL. On this basis he was diagnosed as having hypothyroidism rather than being highly suggestive for myxedema coma. Daily oral levothyroxine 25 μg was initiated and increased to 50 μg 3 days later. Seven days after being started on levothyroxine, the patient suddenly developed impaired consciousness, hypoxemia, hypotension, hypothermia, and hyponatremia. Electrocardiography revealed junctional bradycardia with Osborne J-wave. Myxedema coma was therefore diagnosed. He went into cardiac arrest in the emergency room but was resuscitated. Despite subsequent intravenous administration of hydrocortisone and levothyroxine, as well as intensive supportive care, he eventually died 12 hours after hospital admission. This case illustrates some of the challenges associated with the management of patients with signs highly suggestive/diagnostic of myxedema coma, including the optimal loading dosage and intervention timing of thyroid hormone replacement.

Key words: Signs suggestive of myxedema coma, Osborne J-wave, Hypothermia, Intravenous levothyroxine
Case Report

In December 2020, a 75-year-old man being cared for at a private nursing home was brought to a local hospital with somnolence and generalized edema. He had a history of arteriosclerosis obliterans treated with oral cilostazol and Alzheimer’s disease and schizophrenia without medication. Up to that point, he had been able to have simple conversations, despite his cognitive decline. There was no history of thyroidectomy, previous exposure to radiation, or any personal or family history of thyroid disease. He had a Japan Coma Scale (JCS) score of 20 and a Glasgow Coma Scale (GCS) score of 11 (E2, V4, M5). He was 156.0 cm in height, with a weight of 43.0 kg and a body mass index of 17.7 kg/m². Examination of vital signs showed an axillary temperature of 36.0°C, pulse rate 60 bpm with regular rhythm, blood pressure 102/71 mmHg, respiration rate 16 breaths/min, and oxygen saturation 95% (ambient air). Electrocardiography demonstrated a normal sinus rhythm with a heart rate of 60 bpm and low voltage in the limb leads (Fig. 1A). A chest X-ray demonstrated mild cardiomegaly and a small amount of right pleural effusion (Fig. 1B). Laboratory tests revealed the following values: aminotransferase (AST) 69 U/L (normal range, 13–37 U/L), lactate dehydrogenase (LDH) 303 U/L (normal range, 122–228 U/L), creatine kinase (CK) 293 U/L (normal range, 61–265 U/L), and mild hyponatremia (136.5 mmol/L [normal range, 138–146 mmol/L]). Thyroid studies showed the following values: thyrotropin (TSH) 219.2 μU/mL (normal range, 0.5–5.0 μU/mL), free-triiodothyronine (fT3) 1.0 pg/mL (normal range, 2.3–4.0 pg/mL), and free-thyroxine (fT4) 0.15 ng/mL (normal range, 0.9–1.7 ng/mL). These data are shown in Table 1A. The patient’s condition fulfilled the diagnostic criteria for suspected myxedema coma (3rd draft) stipulated by the Japan Thyroid Association, with hypothyroidism and altered mental status, although the pulse rate was just at the borderline of 60 bpm. However, it was difficult for the physician at the local hospital—who was seeing him for the first time—to assess the changes in his mental state due to the underlying cognitive decline. Therefore, the patient’s reduced responsiveness was initially thought to be attributable to fatigue caused by hypothyroidism superimposed on the underlying cognitive decline. On this basis, he was diagnosed as having hypothyroidism rather than highly suspected myxedema coma, and started on an initial dose of oral LT4 25 µg daily, which was increased to 50 µg 3 days later. After the initiation of thyroid hormone replacement, the patient recovered to an extent that allowed him to respond to simple yes or no questions, equivalent to a GCS score of 13 (E3, V4, M6). However, 7 days after the start of treatment, he was brought to the emergency room (ER) after suddenly developing impaired consciousness, hypothermia, and low oxygen saturation in the morning. The nursing care home staff confirmed that he had been taking the thyroid medication and denied administering any new sedative agents such as benzodiazepines or exposure to cold. On arrival at the emergency room, the patient was obviously very ill, with a GCS score of 6 (E1, V2, M3). His vital signs were as follows: rectal temperature, 24.4°C; pulse rate, 34 bpm with regular rhythm; blood pressure, 58/43 mmHg; respiration rate, 10 breaths/min; and oxygen saturation, 93% (10 liters of oxygen via a simple mask with an attached reservoir). Physical examination revealed bilateral inspiratory wheezing on lung auscultation, periorbital and generalized edema, and no evidence of goiter or prior surgical incision in the neck. Electrocardiography revealed...

Fig. 1 Chest X-ray and electrocardiogram upon admission to a local hospital. (A) The electrocardiogram shows normal sinus rhythm with a heart rate of 60 bpm and low voltage in the limb leads. (B) Chest X-ray shows mild cardiomegaly and a small amount of right pleural effusion.
junctional bradycardia with a heart rate of 30 bpm with Osborne J-wave and low voltage in the limb leads (Fig. 2A). Further examination of his medical history revealed no ischemic heart disease. Chest X-ray demonstrated cardiomegaly, pulmonary congestion, and bilateral pleural effusion (Fig. 2B). Head CT revealed no abnormalities. Laboratory tests yielded the following values: AST 265 U/L (normal range, 13–33 U/L), LDH 639 U/L (normal range, 100–200 U/L), CK 8,677 U/L (normal range, 62–287 U/L), and hyponatremia (128 mmol/L [normal range, 135–149 mmol/L]). Thyroid studies yielded the following: TSH 162 μU/mL
was possible that laryngeal edema may have been caused by hypothyroidism, deterioration of mental status, hypothermia, hypotension, hypoventilation and hyponatremia, a diagnosis of myxedema coma was established. Hashimoto encephalopathy was ruled out due to the simultaneous presence of multiple life-threatening vital signs in addition to the altered mental state. General emergency supportive care was initiated immediately, and intravenous thyroid hormone replacement therapy was prepared. Noradrenaline was administered to maintain blood pressure, and considering the possibility of secondary adrenal insufficiency, 100 mg of hydrocortisone was given intravenously every 8 hours. However, during examination in the ER, the patient suddenly went into cardiac arrest, and cardiac pulmonary resuscitation restored spontaneous circulation in 5 minutes. Intravenous administration of thyroid hormone replacement was promptly performed at a loading dose of 300 μg LT4. Liothyronine (LT3) replacement using a nasogastric tube could not be performed due to tube insertion failure. It was possible that laryngeal edema may have been present because of the severe thyroid hormone deficiency. The patient continued to deteriorate, requiring more vasopressors at a higher dosage. He was also started on empiric antibiotic treatment, without waiting for peripheral blood, sputum, and urine culture results. Despite all of the above measures, the patient failed to respond, and died 12 hours after hospital admission. A few days later, the serum cortisol level in the morning was found to have been 25.6 μg/dL (normal range, 4.5–21.1 μg/dL). Although it was not possible to confirm whether adrenal insufficiency had been present, we considered it to have been unlikely. In addition, all cultures obtained on admission were found to be negative.

Discussion

In the present case, oral LT4 replacement was initiated following an initial diagnosis of hypothyroidism, followed by deterioration to fatal myxedema coma despite dose escalation of LT4. During the procedures in the ER, the patient developed cardiac arrest caused by severe hypothermia complicated by junctional bradycardia with Osborne J-wave on the electrocardiogram. He was successfully resuscitated but eventually not saved. This case raises several important clinical issues, including the possibility that the recommended loading dose for LT4 replacement should be administered immediately after early disease recognition, even if myxedema coma is not immediately confirmed. This case also illustrates the difficulty of diagnosing probable myxedema in patients with cognitive decline.

Recently, a study of the national database in Japan revealed that the incidence of myxedema coma is 1.08 per million per year, with an overall in-hospital mortality rate of 29.5% [6]. Because of its high mortality, immediate initiation of thyroid hormone replacement is essential following early disease recognition based on clinical suspicion by primary care physicians. However, because of its rarity and sudden onset, there are no globally validated diagnostic criteria for myxedema coma, and no single diagnostic test can confirm or exclude the diagnosis. In Japan, the original diagnostic criteria for myxedema coma stipulated by the Japan Thyroid Association and available on the internet have been widely adopted, but have not been validated [5]. Briefly, the criteria include several elements such as hypothyroidism, central nervous system failure, hypothermia, hypoventilation, circulatory failure, and hyponatremia. So far, one study from the United States has reported a diagnostic scoring system for myxedema coma that is useful for early recognition of the illness [7]. The elements assessed included evidence of thermoregulatory dysfunction, central nervous system effects, gastrointestinal symptoms, cardiovascular dysfunction, metabolic disturbances, and the presence of a precipitating event. This system uses a grading scale of 0 to 30 for each element. A score of 60 or higher is highly suggestive/diagnostic for myxedema coma, a score of 25–59 suggests a risk for myxedema coma, and a score below 25 suggests that myxedema coma is unlikely. In that report, all of 14 patients diagnosed as highly suggestive/diagnostic for myxedema coma had both hypothyroidism and deterioration of mental status, while only 1 of 7 patients in whom myxedema coma was ruled out had these two diagnostic criteria.

Recently, one retrospective observational study from India has reported a treatment protocol for oral LT4 replacement in patients diagnosed as having myxedema coma based on this diagnostic scoring system [8]. The notable feature of this protocol was that even patients with myxedema scores of 25–59 were given oral LT4 replacement with a dose of at least 250–300 μg based on assessment of cardiovascular dysfunction. Fourteen patients diagnosed with myxedema coma, all of whom had central nervous system manifestations and a median serum TSH level of 67.5 μU/mL (range 10.02–100.00 μU/mL), were included. There was no correlation between the myxedema score and the serum TSH or free-T4 level. With this regimen, 13 patients survived, and only 1 patient died. Four of the 14 patients had a myxedema coma score of 25–59, indicating a possible risk for myxedema coma, and all of them survived when
<table>
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<th>Table 1B Laboratory findings on admission to our hospital</th>
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<tr>
<td><strong>Blood cell count</strong></td>
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<tr>
<td>WBC 4.77 × 10^3/μL (4.0–9.0) GGT 8 U/L (11–58) Neutrophil 93.90% (44.0–74.0) TP 5.5 g/dL (6.6–8.7)</td>
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<td>Eosinophil 0% (1.0–5.0) Alb 3.1 g/dL (3.4–4.8) Basophil 0% (0.0–1.0) BUN 15 mg/dL (5–23)</td>
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<td>Lymphocyte 3.80% (20.0–43.0) Cre 0.49 mg/dL (0.36–1.06) Monocyte 2.30% (3.0–9.0) T-cho 182 mg/dL (125–220)</td>
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<td>RBC 377 × 10^6/μL (450–510) Na 128 mmol/L (135–149) Hb 11.1 g/dL (12.0–16.0) K 3.6 mmol/L (3.5–4.9)</td>
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<td>Ht 31.70% (39.0–52.0) Cl 95 mmol/L (96–108) MCV 84.1 fL (90–105.0) Ca 8.1 (8.1–10.4)</td>
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<td>Platelet 3.9 × 10^4/μL (15.0–45.0) UA 3.8 mg/dL (3.4–7.0) Amilase 222 U/L (33–120)</td>
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<td>Coagulation CK 8,677 U/L (62–287) PT-INR 1.27 (0.8–1.3) CK-MB 529 U/L (0–24) APTT 45.4 sec (24.0–36.0) Troponin T 0.075 ng/mL (0.000–0.100)</td>
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<td>FDP 5.8 μg/mL (&lt;5.0) Glucose 93 mg/dL (60–110) D-dimer 1.6 μg/mL (&lt;1.0) HbA1c 5.30% (4.6–6.2)</td>
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<td>Arterial blood gas NH3 21 μg/dL (30–86) PH 7.39 (7.35–7.45) PO2 54 mmHg (80–90) TSH 162 μU/mL (0.54–4.54)</td>
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<td>PCO2 44 mmHg (35–45) Endocrine and immunology HCO3 26 mmol/L (22–26) fT3 0.72 pg/mL (2.20–4.30)</td>
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<td>O2 saturation 87.50% (92–96) fT4 0.2 ng/dL (0.90–1.70) Lactate 17.2 mg/dL (4.0–20.0) TSH-R-Ab 0.501 U/L (0–2.0)</td>
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<td>Biochemistry TG-Ab 7.87 U/mL (0.0–16.0) TPO-Ab 25.6 μg/dL (4.5–21.1) T-Bil 0.5 mg/dL (0.2–1.2) Cortisol 0.00–0.30)</td>
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<td>T-Bil 0.5 mg/dL (0.2–1.2) Cortisol 25.6 μg/dL (4.5–21.1) AST 265 U/L (13–33) ALP 8 U/L (8–42) Cultures</td>
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<td>ALT 81 U/L (8–42) Blood negative ChE 120 U/L (168–470) Blood negative LDH 639 U/L (100–200) Sputum negative</td>
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<td>ALP 8 U/L (115–359) Urine negative</td>
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Parentheses: Reference Values

WBCs, white blood cells; RBCs, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; FDP, fibrin degradation product; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; ChE, choline esterase; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; UA, uric acid; CPK, creatine phosphokinase; CRP, C-reactive protein; TSH, thyrotropin, fT3: free-triiodothyronine, fT4: free-thyroxine, Anti TSH-R Ab: anti-thyrotropin receptor antibody, Anti TPO Ab: anti-thyroid peroxidase antibody, Anti TG Ab: antithyroglobulin antibody
the proposed treatment protocol for oral LT4 replacement was adopted. Using this system, the score for our present patient was 40 at the time of presentation at the local hospital, which suggested a risk for myxedema coma. However, in Japan, even if patients suggested to be at risk for myxedema coma are identified, there is still no established management strategy. Analysis of the national inpatient database in Japan showed that the maximal daily dosage of LT4 did not significantly affect mortality due to myxedema coma [6]. Approximately one-fourth of 149 patients with myxedema coma received a LT4 dosage of 100 μg or lower. However, the authors consider that because of the small sample size and unknown severity of the myxedema coma, these results would not have been able to provide recommendations regarding the optimal dosage for thyroid hormone replacement. The American Thyroid Association task force has recommended that initial thyroid hormone replacement for myxedema coma should be intravenous LT4 at a loading dosage of 200–400 μg with or without levothyroxine (LT3) [9]. Even if our present patient had been diagnosed as highly suggestive for myxedema coma using the Japanese criteria (hypothyroidism, altered mental status, and a pulse rate just at the borderline of 60 bpm), it is considered that the recommended loading dose of LT4 should have been administered immediately. To make effective use of intravenous LT4, we consider it necessary to establish management strategies for myxedema coma, including patients who are thought highly likely to be at risk.

Our present patient demonstrated an inverted T wave in V2-6 in addition to junctional bradycardia with Osborne J-wave on the electrocardiogram despite having no history of ischemic heart disease, in addition to elevated levels of CK, CK-MB, and troponin. Many hypothyroid patients have high serum CK concentrations. The isoenzyme distribution is almost completely MM, with less than 4% constituting MB, indicating a skeletal muscle, not myocardial, origin [10]. However, as many as 14% of patients with hypothyroidism have a raised serum concentration of CK-MB, which can be confusing for evaluation of ischemic heart diseases [11, 12]. Similar biochemical findings have previously been reported in patients with myxedema coma without infarction, and are probably the result of hypothermia in combination with hypothyroidism-induced reduction in cardiac enzyme turnover [13]. This problem is obviated by measurement of the serum troponin level, which is normal in hypothyroidism [11]. Furthermore, elevation of CK-MB can have non-cardiac causes such as hypothermia [14, 15]. While hypothermia has been noted to increase CK-MB levels, the mechanism remains poorly understood [16]. On the other hand, Sawalha et al. reported a patient with mild hypothermia in whom other potential causes of elevated CK-MB and troponin were ruled out [17]. Although the above case and the present case had limitations, specifically in terms of ruling out other etiologies, hypothermia could also be considered as a cause of elevated CK-MB and troponin levels.

Many patients with myxedema coma have hypothermia, due to the decrease in thermogenesis that accompanies depressed metabolism. The severity of the hypothermia is related to mortality; the lower the temperature, the more likely a patient is to die. Severe hypothermia (body temperature <28°C) is specifically associated with a high risk of sudden cardiac arrest [18]. Hypothermia causes characteristic ECG changes because of slowed impulse conductation through potassium channels. This results in prolongation of all the ECG intervals, including RR, PR, QRS, and QT [19]. There may also be an elevation of the J point (only if the ST segment is unaltered), producing a characteristic Osborn J-wave that represents a distortion of the earliest phase of membrane repolarization [20-22]. The height of the J wave is roughly proportional to the degree of hypothermia. Similarly, in severe hypothyroidism, decreased expression of tri-iodothyronine (T3) in heart cells can compromise cardiac contractility, resulting in a decreased heart rate, slower conduction of electrical stimuli in the heart muscle, and an increase in systemic vascular resistance. This may cause cardiac arrhythmias, the most common conduction abnormalities being sinus bradyarrhythmia, heart block, ventricular tachycardia, and torsades de pointes [23, 24]. Graham et al. reported that although junctional bradycardia in accidental hypothermia was rare (5.5%), 3 of their 4 patients with this rhythm died [21]. Two cases of myxedema coma showing Osborne J-wave on the electrocardiogram have been reported so far [25, 26]. One of the two patients, who had severe hypothermia, was saved by hormone replacement and passive external rewarming [25]. Another patient with moderate hypothermia was successfully managed by veno-arterial extracorporeal blood rewarming [26]. In the present case, as the patient developed cardiac arrest caused by severe hypothermia with a rectal temperature of 24.4°C complicated by junctional bradycardia with Osborne J-wave on the electrocardiogram during the ER procedures, we consider that life-saving would have been difficult. However, aggressive rewarming interventions based on the severity of hypothermia, such as the extracorporeal blood rewarming mentioned above, could be considered.

In conclusion, myxedema coma is a rare medical emergency associated with a high mortality rate. To improve the outcome of patients with myxedema coma in similar settings and in the presence of diagnostic criteria but in the absence of treatment strategies, early
diagnosis and adoption of suitable management strategies are recommended. Furthermore, when encountering an unexplained altered state of consciousness in patients with cognitive decline, physicians should consider the possibility of potential myxedema coma and be prepared to initiate adequate replacement of the underlying thyroid hormone deficiency.

**Disclosure**

The authors state that they have no conflicts of interest.

**References**