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## A “cold” case of myxedema coma

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**Abstract**

Myxedema coma (MC) represents a rare and severe manifestation of the extreme degree of longstanding and decompensated hypothyroidism. This condition affects approximately 0.22 cases per million inhabitants per year, especially women and the elderly, and its mortality remains very high, approximately 30-50%. This condition can present with altered mental status, hypothermia, bradycardia, hyponatremia, cardiomegaly, decreased cardiac output, and hypotension. Sometimes myxedema can cause respiratory depression and gastrointestinal issues like anorexia, abdominal pain, constipation, fecal retention, and paralytic ileus. These multiple clinical manifestations represent a true diagnostic challenge. MC can occur in patients with undiagnosed or undertreated hypothyroidism, and it may remain undiagnosed due to the sudden onset, the lack of reliable history in patients presenting with altered sensorium, and the overlap of symptoms with common medical conditions like sepsis, metabolic encephalopathy, and cerebrovascular events. Prompt recognition and management of MC are crucial to reducing the risk of life-threatening complications and improving patient outcomes.

## Introduction

Myxedema coma (MC) represents a rare and severe manifestation of the extreme degree of longstanding and decompensated hypothyroidism. This condition affects approximately 0.22 cases per million inhabitants per year, especially women and the elderly, and its mortality remains very high, approximately 30-50%.<sup>1</sup>

This condition can present with altered mental status, hypothermia, bradycardia, hyponatremia, cardiomegaly, decreased cardiac output, and hypotension.<sup>2,3</sup> Sometimes myxedema can cause respiratory depression and gastrointestinal issues like anorexia, abdominal pain, constipation, fecal retention, and paralytic ileus.<sup>4</sup>

These multiple clinical manifestations represent a true diagnostic challenge, and the same term myxedema “coma” can be a misnomer, considering that the altered mental status can range from confusion to lethargy or obtundation to coma. Less frequently, cases of MC have been described in patients who are debutants with hypothyroidism, so it is important to investigate a thorough history comprising thyroid surgery, medication history, and compliance with medication.<sup>5</sup>

Triggers such as cold exposure, stroke, heart failure, acute myocardial infarction, infectious processes and sepsis, trauma, electrolyte imbalances, poor medication compliance, and drugs can precipitate myxedema.<sup>6-8</sup>

Between drugs, amiodarone is notably associated with thyroid dysfunction (in 15-20% of patients),<sup>9</sup> usually from 3 months to 2 years after initiation.<sup>10</sup>

Instances of MC in patients under amiodarone therapy without a previous thyroid disease history have been documented.<sup>11</sup>

As the disease is rare and unrecognized, and there is a paucity of randomized controlled trials in the field of myxedema crisis and its therapy, the current recommendations are based on reports of case series and expert opinions.<sup>1</sup> Nevertheless, the basis of treatment of MC remains hormone replacement (levothyroxine or a combination of levothyroxine and triiodothyronine) and hydrocortisone until possible concomitant adrenal insufficiency is ruled out. Besides electrolyte correction, supportive therapies, and treatment of underlying precipitant conditions must be managed.<sup>7,12</sup>

Hypotension, bradycardia at presentation, need for mechanical ventilation, hypothermia unresponsive to treatment, sepsis, intake of sedative drugs, lower Glasgow Coma Scale (GCS), and high Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores were found to be significant predictors of mortality in mixededema crisis.<sup>13</sup> Studies have also shown that higher doses of T3 are associated with increased mortality, and lower doses of T3 and T4 may be associated with a favorable prognosis. Other factors associated with mortality include advanced age and cardiovascular disease.<sup>14,15</sup>

## Case Report

We present a case of a 77-year-old male who was brought into the emergency room as a suspected stroke for the onset of dysarthria and altered state of consciousness.

On medical examination, the patient was less responsive with a GCS of 10/15, hypothermic (body temperature 30°C), hypotensive (blood pressure 80/60 mmHg), bradycardic (45 bpm), diffuse non-pitting edema. Oxygen saturation on pulse oximetry was unrecordable. On the electrocardiogram (ECG), junctional rhythm was observed. Chest examination revealed bibasal fine crepitation and the bed-side ultrasound showed bibasal B pattern, no pleural effusion, no free abdominal fluid, right kidney with cortical thinning (known finding), no left hydronephrosis.

External warming, volume resuscitation with warm fluid and subsequent circulatory support with norepinephrine were performed, in the suspicion of severe sepsis in anergic patient. So, the patient was admitted to our internal medicine department (UOC Interna Medicina, Parma University Hospital).

His past medical history was significant for Alzheimer's disease (diagnosed in 2008), chronic renal failure (baseline creatinine of 2 mg/dL), ischemic cardiomyopathy with hypokinetic-dilated heart

due to previous ST elevation myocardial infarction (STEMI) (in 2018), and paroxysmal supraventricular tachycardia, for which amiodarone therapy was initiated.

He also normally took bisoprolol 2.5 mg once at night, aspirin 100 mg, atorvastatin 40 mg once at night, furosemide 25 mg once in the morning, canrenone 50 mg once in the morning and memantine 10 mg once in the morning.

He did not have any evidence of a known thyreopathy.

Given the ECG findings, amiodarone,  $\beta$ -blockers and memantine were discontinued, with restoration of a sinus bradycardia with a heart rate of 38-40 bpm.

The arterial blood gas analyses on 21% fraction of inspired oxygen showed mild hypoxemia, so he was put on 2 L of oxygen *via* nasal cannula. His admission blood tests showed a mild rise of inflammatory markers, increased transaminases, abnormalities of the blood count, including mild anemia, moderate thrombocytopenia, and signs of acute-on-chronic kidney failure (Table 1).

At the beginning, we approached the patient as having severe sepsis, so we continued fluid resuscitation, aminergic support, and antibiotics (piperacillina/tazobactam), with effective hemodynamic stabilization. Due to such a high thyroid stimulating hormone (TSH) value and the persistence of hypothermia, somnolence and bradycardia, he was discussed with the Endocrinologist regarding the probability of MC as a contributing factor of the clinical condition. The Myxedema coma Score at our evaluation was 70 (Table 2). He was commenced on low-dose oral levothyroxine (LT4) of 50 mcg, preceded by the administration of stress doses of intravenous hydrocortisone, subsequently tapered and switched to a maintenance oral dosage. Oral LT4 was gradually increased to 75 mcg daily. In the following days, there was a progressive improvement in heart rate (75-80 bpm) and body temperature (36-36.5°C). Vigilance also improved, within the limits of a patient with already known severe cognitive decline due to Alzheimer's dementia, making it possible to start physiotherapy.

To investigate anemia and thrombocytopenia, we screened hemolysis indices (in range), and both esophagogastroduodenoscopy and abdominal computed tomography (CT) scans were negative for bleeding. After transfusion of one unit of red blood cells, the hemoglobin values remained stable without further need for blood transfusion. Antiplatelet antibodies were positive; however, no recommendations were made by Hematologists given the spontaneous increase in values until the lower limits of the normal range.

The last thyroid function assessment before discharge showed a significant improvement: TSH 32 uU/mL with free thyroxine (FT4) 0.56 ng/dL. The patient was then transferred to another hospital to continue the rehabilitation cycle.

## Discussion

MC is a rare life-threatening complication of severe hypothyroidism. It can occur in patients with undiagnosed or undertreated hypothyroidism, and it may remain undiagnosed due to the sudden onset, the lack of reliable history in patients presenting with altered sensorium, and the overlap of symptoms with common medical conditions like sepsis, metabolic encephalopathy, and cerebrovascular events.<sup>16</sup>

Our patient was affected by Alzheimer's disease without a known history of hypothyroidism, which made the diagnosis even more insidious due to the pre-existing cognitive decline. He was initially treated as septic shock with the administration of fluid resuscitation, antibiotics, and vasopressors, showing an initial clinical response and improvement in his level of consciousness. The suspicion of underlying severe hypothyroidism arose only in the following days due to the persistence of bradycardia, maintenance of body temperature around 35°C, and significant psychomotor slowing, along with the anamnesis of amiodarone use in the home therapy.

For this reason, in our case, we consulted the Endocrinologist only after obtaining a definitive laboratory confirmation of overt severe hypothyroidism (TSH 124 uU/mL, FT4 0.28 ng/dL).

For the management of MC, American Thyroid Association endorses the use of intravenous LT4 and glucocorticoids irrespective of the severity of disease,<sup>17</sup> although randomized clinical trials are still lacking and not realistic since the rarity and severity of the disease, so the recommendations

regarding the type and route of replacement therapy are based on expert opinions and isolated case reports.

Due to the limited availability of intravenous LT4 in many countries most of the patients are managed with oral LT4. Several observational studies have shown oral LT4 to be equally efficacious as intravenous.<sup>13,18,19</sup> In particular, one of the largest single-center studies demonstrated that there was no statistically significant difference in efficacy between groups who received intravenous LT4 vs oral LT4 in patients with Myxedema Score <90, while intravenous LT4 should be the preferred treatment in patients with Myxedema Score >90.<sup>20</sup> Indeed, mortality increased markedly above a Myxedema Score of 90 (83.33%) and was 100% above a Myxedema Score of 110.<sup>20</sup>

Nevertheless, the oral LT4 doses proposed in different studies typically included a loading dose (250-500 mcg) followed by a maintenance dose around 1,6 mcg/kg.<sup>18,20,21</sup> Lower doses have been reported in case reports where oral LT4 was combined with liothyronine.<sup>22</sup>

However, randomized controlled trials comparing the efficacy of two treatment modalities are needed to make robust conclusions.

Besides the known factors predicting mortality (hypotension, bradycardia at presentation, need for mechanical ventilation, hypothermia unresponsive to treatment, sepsis, intake of sedative drugs, lower GCS, and high APACHE II scores),<sup>5,13</sup> there is evidence that rapid increases in serum thyroid hormone concentrations in long-standing hypothyroidism are associated with higher risks of inducing myocardial infarction or arrhythmias.<sup>23,24</sup> Also, higher age and use of catecholamines (with or without steroids) were significant predictors of in-hospital mortality in MC, and cardiovascular collapse is the most common cause of death in MC.<sup>2,25</sup> So the gradual increases in plasma T4 and T3 by enteral administration of thyroid hormones could result in slower cardiovascular responses compared with intravenous administration.<sup>26</sup>

However, no protocol is available for the administration of oral LT4 in MC.

The advantages of intravenous administration are early saturation of binding sites with a rapid replenishment of the thyroid hormone pool. Oral LT4 is generally not advised because of the unpredictability of gastrointestinal absorption in this condition. In addition, difficulties with the insertion of a nasogastric tube (due to potential concomitant macroglossia and airway edema) are another factor that may preclude the use of oral LT4 in MC.<sup>18</sup>

In our case, the decision to start with a low dose of oral LT4 rather than a high dose of intravenous LT4, regardless of its unavailability in our country, was justified by the patient's clinical improvement after sepsis treatment, thus indicating sepsis as the trigger of the clinical presentation. Moreover, the patient's underlying cardiological condition (ischemic cardiomyopathy with hypokinetic-dilated heart due to previous STEMI) could have exposed him to a higher risk of potential further ischemic events or arrhythmias. Furthermore, the not excessively high Myxedema Score (score of 70) at the time of evaluation also influenced our therapeutic strategy.

We chose to complement the therapy with corticosteroids, given the concomitant sepsis and tendency towards hypotension. The continuation of this therapy with gradual tapering was instead justified by the finding of adrenal hyperplasia on the CT scan, which could suggest an ongoing adrenal insufficiency in the context of acute illness.

The real innovation in our case was starting replacement therapy with oral LT4 without a loading dose (initial dose of 50 mcg gradually increased to 75 mcg), which could have exposed our extremely fragile patient to cardiovascular complications. Nonetheless, we achieved a gradual improvement in the patient's vital signs and clinical condition.

Another interesting observation is represented by anemia and thrombocytopenia, which later returned to the normal range without specific therapy. These findings have already been described in the literature and reported to be the result of bone marrow hypoplasia in the context of severe hypothyroidism, showing how pancytopenia could be a part of the multisystemic complication of this condition.<sup>27</sup> The robust response after only one unit of packed red blood cells and the low count of reticulocytes supported this theory.

## **Conclusions**

Diagnosis of MC is intricate due to the subtle symptoms and further complicated in elderly patients with a history of cardiac diseases. Prompt recognition and management of MC are crucial to reducing the risk of life-threatening complications and improving patient outcomes.

The main stone of the therapy is represented by the combination of LT4 and glucocorticoids, and we suggest following the most robust guidelines of intravenous LT4 despite the potential disadvantages. However, our and other cases showed that oral substitution therapy can represent a valid alternative, even with lower doses of LT4.

Especially in our case, we aimed to provide evidence to highlight the possibility of finding, through future large-scale studies, alternative therapeutic options that might be more appropriate in older and fragile patients to reduce potential cardiovascular implications.

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**Table 1. Blood test at admission and during the follow-up.**

Blood test	Admission	Day 15	Day 25	Normal range
Hemoglobin, g/dL	12.2	9.1	8.6	13.5-18
White cell count	3.61*10 <sup>3</sup> /uL	6.61	8.37	4.2-6*10 <sup>3</sup> /uL
Platelet count	66*10 <sup>3</sup> /uL	64	134	150-400*10 <sup>3</sup> /uL
C reactive protein, mg/L	26	24	/	0.5-5
Prothrombin time	1.08	/	1.19	0.86-1.20
Sodium (Na), mmol/L	141	148	142	135-148
Potassium (K), mmol/L	4.9	3.4	4.2	3.5-5.3
Urea, mg/dL	112	57	36	10-50
Creatinine, mg/dL	2.3	1.8	1.5	0.5-1.4
TSH, uU/mL	124.3	72.5	32.1	0.4-4.0
Free T4, ng/dL	0.28	0.34	0.56	0.60-1.10
Creatin kinasi, U/L	286	/	28	0-200
Cortisol, ug/dL	71	20.4	28.3	6,7-23,0
Bilirubine, mg/dL	0.6	1.1	1.2	0.1-1.1
AST, U/L	109	/	14	0-40
ALT, U/L	148	/	19	0-40
Troponin, ng/L	16	/	/	2.3-17.8

AST, aspartate aminotransferase; ALT, alanine transaminase.

**Table 2. Score for myxedema coma diagnosis.**

Characteristic			Score*
Temperature	>95 degrees F (>35 degrees C)		0
	89.6-95 degrees F (32-35 degrees C)		10
	<89.6 degrees F (<32 degrees C)		20
CNS symptoms	Absent		0
	Somnolence/lethargy		10
	Obtundation		20
	Coma/seizure		30
GI findings	Anorexia/abdominal pain/constipation		5
	Reduced intestinal motility		15
	Paralytic ileus		20
Precipitating factor	Absent		0
	Present		10
Cardiovascular findings	Bradycardia	Absent	0
		50-59 beats/minute	10
		40-49 beats/minute	20
		<40 beats/minute	30
	Other ECG changes**		10
	Pleural/pericardial effusions		10
	Pulmonary edema		15
	Cardiomegaly		15
	Hypotension		20
Metabolic dysfunction	Hyponatremia		10
	Hypoglycemia		10
	Hypoxemia		10
	Hypercapnia		10
	Decreased GFR		10

CNS, central nervous system; ECG, electrocardiogram; GFR, glomerular filtration rate; GI, gastrointestinal.  
 \*Score of ≥60 highly suggestive, score of 25-59 suggestive of risk, and score of < 25 unlikely diagnosis of myxedema coma; \*\*QT prolongation, low voltage complexes, bundle branch blocks, nonspecific ST-T changes, or heart blocks.