An elderly woman with drug-induced coma in winter

A 64-YEAR-OLD WOMAN is admitted to the hospital in mid-December. Her primary physician had treated her successfully for an apparent upper respiratory tract infection 4 weeks previously. Her family reports that since the infection she has been noticeably less active, lacks interest in things that she previously enjoyed, generally feels lethargic, and has never returned to the level of function she had before the infection.

Past medical history. The patient has long-standing hypertension, which is well controlled with amlodipine and bendroflumethiazide.

Initial evaluation. The patient appears lethargic; however, she performs within normal limits on the Mini-Mental State Examination.

Differential diagnosis

1 The differential diagnosis includes which of the following?

- Dementia
- Chronic fatigue syndrome
- Major depression

Dementia is not likely because the patient has been ill for only approximately 1 month. In addition, her cognitive function is not impaired, as shown by her performance on the Mini-Mental State Examination.

Chronic fatigue syndrome. The patient's symptoms do not meet the diagnostic criteria for chronic fatigue syndrome, ie, fatigue for at least 6 months plus at least four of the following:

- Impaired short-term memory or concentration
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multijoint pain without joint swelling or tenderness
- Unrefreshing sleep
- Postexertional malaise lasting more than 24 hours.

Major depression is the diagnosis that is most consistent with the history, as the patient is elderly, recently ill, lacks motivation and interest in previously enjoyed activities, and has been admitted in the winter. However, one should remember that an apparent mood disorder could be due to an underlying physical illness.

2 Which of the following should be considered in the differential diagnosis of an acute confusional state?

- Adverse drug reaction
- Hyponatremia
- Hypoglycemia
- Infection
- Ethanol withdrawal
- Hypothyroidism
- All of the above

The patient is unconscious, cold, bradycardic, and hypotensive.

The differential diagnosis of a recent change in mental status is extensive and must include all of the above possibilities.
The patient's condition worsens
During the next 12 hours, the patient's condition rapidly deteriorates. Her blood pressure falls and she becomes unresponsive. Resuscitative measures are initiated, and she is transferred to the emergency department for further evaluation. Twenty-four hours after the initial hospital admission she is referred to the general medicine service.

Physical examination. The patient is unconscious and has a Glasgow coma score of 5 (of a possible 15; in this rating scale a lower score indicates more profound unconsciousness). Her facial features are puffy and coarse. Her skin is dry and cold. Her heart rate is 48 beats per minute, blood pressure 80/40 mm Hg, and temperature 33.8°C (92.8°F).

The patient's blood sugar level is 90 mg/dL, as measured at the bedside and not necessarily fasting. A 12-lead electrocardiogram reveals sinus bradycardia, a prolonged P-R interval, and symmetric T-wave inversion anterolaterally.

The patient's clinical features are consistent with severe decompensated hypothyroidism (myxedema; Table 1).1-4 Because of the life-threatening nature of the tentative diagnosis and the patient's condition, we began thyroid hormone replacement therapy empirically before laboratory results were available.

FURTHER DIAGNOSTIC TESTING

What is the most important diagnostic test to obtain at this point?

- A complete metabolic panel including renal and liver function profiles and calcium level
- A transthoracic echocardiogram
- A magnetic resonance image (MRI) of the brain
- Thyroid-stimulating hormone (TSH) and free-thyroxine (T4) levels
- A cosyntropin stimulation test

TSH and free T4 levels are needed to confirm the diagnosis of hypothyroidism and are the most important diagnostic tests at this point. This patient's values are:
- TSH 58 IU/L (normal range 0.5-5.0)
- Free T4 1.0 pmol/L (normal range 12-30).

A complete metabolic panel is useful to corroborate the clinical findings but is unlikely to yield a final diagnosis. The patient's values are:
- Sodium 116 mmol/L (normal range 136-142)
- Potassium 2.4 mmol/L (normal range 3.5-5.0)
- Blood urea nitrogen 13.7 mg/dL (normal range 8-23)
- Creatinine 0.9 mg/dL (normal range 0.6-1.2)
- Glucose 133.3 mg/dL (normal range 70-110)
- Serum osmolality 245 mOsm/kg H2O (normal range 275-295).

Hyponatremia with low serum osmolality is characteristic of hypothyroidism and should respond to thyroid hormone replacement therapy with fluid restriction. Hyponatremia may be due to reduced free water clearance, reduced renal blood flow and glomerular filtration, and elevated plasma vasopressin levels.1-4 Thiazide diuretics, which our patient takes, may also contribute to hyponatremia.
Hypoglycemia occurs in hypothyroidism because insulin sensitivity increases while gluconeogenesis and glycogenolysis decrease.\(^1\)\(^4\) (This patient, however, does not appear to have hypoglycemia.)

Other tests, as described in the following section, may be indicated as well, in view of the features of severe decompensated hypothyroidism.

Features of severe decompensated hypothyroidism

Respiratory depression is characteristic of severe decompensated hypothyroidism as a result of respiratory muscle weakness and upper airway obstruction due to an enlarged tongue and myxedematous infiltration of the upper airway. Consequently, hypoxia, hypercapnia, and hypoventilation with CO\(_2\) retention occur. This patient’s arterial blood gas values while receiving oxygen at 4.0 L/minute per nasal cannula are:

- \(\text{pH} \ 7.39\) (normal range 7.35–7.45)
- \(\text{PaCO}_2\) 46.5 mm Hg (normal range 35–45)
- Bicarbonate 26.1 mmol/L (normal range 21–28)
- Base excess 2.6 mmol/L (normal range -2–+2).

Defective thermoregulation is also characteristic of myxedema coma. Thyroid hormone exerts its action by stimulating calorigenesis via sodium/potassium-ATPase.

Cardiac features include bradycardia, heart block, diastolic hypertension, cardiomegaly, and T-wave flattening or inversion. Cardiac enzymes may be elevated as a result of increased muscle membrane permeability and reduced metabolic clearance; this patient’s cardiac enzyme levels, which peaked on her second hospital day, were:

- Total creatine kinase 2,393 U/L (normal range 50–200)
- Creatine kinase-MB fraction < 2% (normal < 6)
- Aspartate aminotransferase 148 U/L (normal range 20–48).

The electrocardiographic and cardiac enzyme changes may suggest an erroneous diagnosis of acute myocardial infarction (MI). However, in severe hypothyroidism without acute MI, the troponin I level remains normal.\(^5\) For practical purposes, normal troponin I levels exclude a full-thickness MI, but troponin I levels may be normal with non-Q-wave MIs. If an MI is suspected, an echocardiogram may be useful if it shows regional wall motion abnormalities, but a normal echocardiogram will not exclude the diagnosis of MI. Echocardiography will also diagnose a pericardial effusion, which may occur in myxedema.

Adrenal hypofunction is vital to consider following a diagnosis of severe hypothyroidism. Central hypothyroidism may be associated with adrenocorticotropic hormone deficiency, and primary hypothyroidism may be associated with primary adrenal insufficiency (Schmidt syndrome). Starting thyroid hormone replacement without also giving steroids (hydrocortisone) may precipitate adrenal crisis. Appropriate use of steroids is also important because thyroxine increases cortisol clearance.

Determining the Cause of Hypothyroidism

Thyroid antibody tests, magnetic resonance imaging of the pituitary, and pituitary function tests help identify the cause of the hypothyroidism. This patient’s baseline pituitary function values were:

- Prolactin 48 µg/L (normal range 1–25)
- Growth hormone 308 pmol/L (normal range < 880)
- Follicle-stimulating hormone (FSH) 61 IU/L (normal range 1–100)
- Luteinizing hormone (LH) 53 IU/L (normal range 6–30).

The mild hyperprolactinemia is consistent with a diagnosis of primary hypothyroidism. However, thioridazine can elevate prolactin levels, so this possibility cannot be completely ruled out. The growth hormone level is within normal limits, and the FSH and LH levels are consistent with the patient’s postmenopausal status.

A brain MRI did not show any pituitary adenoma or hypothalamic lesion. A cosyntropin stimulation test was negative, as were texts for antithyroglobulin and adrenal cortex antibodies. A test for thyroid microsomal antibodies was positive at a dilution of 1:350, in myxedema, the ECG and cardiac enzymes may falsely suggest MI.
Starting thyroid hormone without steroids can precipitate adrenal crisis

consistent with a diagnosis of chronic autoimmune thyroiditis (Hashimoto thyroiditis).

Hashimoto thyroiditis or chronic autoimmune thyroiditis is the most common cause of primary hypothyroidism. It commonly presents as a painless goiter (but a goiter may be absent) in an elderly woman. The etiology is unknown. It is characterized by lymphocytic infiltration and destruction of the thyroid follicular cells. Thyroid autoantibodies (antimicrosomal antithyroglobulin antibodies) are present in 80% of cases. It may be associated with Grave disease, vitiligo, myasthenia gravis, type 1 diabetes mellitus, Addison disease, pernicious anemia, and other autoimmune diseases.

**WHAT FACTORS CAN PRECIPITATE MYXEDEMA COMA?**

4 Which of the following can precipitate myxedema coma?

- Drugs
- Noncompliance with thyroid replacement therapy
- Cold exposure
- Infection

A number of factors may precipitate coma in hypothyroid patients, including the use of diuretics, sedatives, or tranquilizers; severe infections; surgery or trauma; myocardial infarction; cerebrovascular accident; gastrointestinal bleeding; cold exposure; and missing doses of thyroid hormone therapy (TABLE 2).

**TREATMENT OF MYXEDEMA COMA**

5 Which of the following forms of thyroid hormone therapy and routes of administration is best for the initial treatment of myxedema coma?

- Levothyroxine (T₄, Synthroid) by mouth
- Liothyronine (T₃, Cytomel) by mouth
- Levothyroxine intravenously
- Liothyronine intravenously
- Both levothyroxine and liothyronine intravenously

Thyroid hormone replacement is the definitive treatment for myxedema coma, but there is no agreement as to dosage or what form of thyroid hormone is most effective in this situation. Prospective, randomized, controlled clinical trials to identify the most effective form are lacking because this condition is rare. Thus, therapy must be individualized.

**Intravenous administration preferred.** Because hypotension and intestinal ileus occur in myxedema coma, intravenous therapy is preferred. Although levothyroxine has been successfully given via nasogastric tube for myxedema coma, its oral bioavailability is unpredictable (50%–80%).

**Which hormone to give?** Liothyronine (T₃) is the biologically active form, and levothyroxine (T₄) is converted to T₃ in vivo. For immediate thyroid hormone action, liothyronine is ideal: it binds serum proteins to a lesser extent than levothyroxine and has a larger volume of distribution and a shorter half-life. However, intravenous liothyronine requires multiple dosing, is expensive, and may account for increased mortality compared with intravenous levothyroxine in the treatment of myxedema coma. Thus, most endocrinolo-
The initial treatment of myxedema coma is controversial

gists recommend initial therapy with intravenous levothyroxine alone. However, both levothyroxine and liothyronine can be initially given alone or in combination.

Dosage. In giving thyroid hormone replacement, one should keep in mind that thyroxine-binding proteins have a large binding capacity, and that it is necessary to saturate these proteins to provide an effective circulating level of free T₄. On the other hand, we must keep in mind the danger of inducing coronary ischemia, arrhythmias, and sudden death.

Corticosteroids. As noted earlier in our discussion of the adrenal hypofunction that often accompanies severe hypothyroidism, it is important to give steroids (hydrocortisone) when starting thyroid hormone replacement therapy, to avoid precipitating an adrenal crisis.

The patient recovers

The patient was given intravenous fluids restricted to 1 liter per day, intravenous flumazenil, passive rewarming, and intravenous hydrocortisone, levothyroxine, and liothyronine. (Both thyroid hormones were given, in the absence of hard data, on the basis of our personal preference and because the patient was felt to have severe hemodynamic instability.) After 48 hours of this treatment, she regained consciousness. She continued taking levothyroxine by mouth. She remained intermittently disoriented over the course of the next 2 weeks, but by the third week of hospitalization, she was fully alert.

She was discharged home taking 75 μg of levothyroxine per day. She remains well 1 year after the hospitalization and continues to be followed every 6 months.

■ REFERENCES


■ LESSONS FROM THIS CASE

This case illustrates the varied presentation of hypothyroidism, which can include depression, particularly in the elderly. The patient had no previous history of thyroid disease. Yet, the disease progressed rapidly, probably triggered by a number of factors including infection and sedatives. She also had an altered level of consciousness, hypotension, bradycardia, hypothermia, and hyponatremia.

This case also demonstrates the importance of rapid TSH assays in confirming the diagnosis. In about 90% of cases of myxedema, the TSH level is elevated. However, the TSH level may be normal or low in myxedema that results from pituitary or hypothalamic pathology (central hypothyroidism) or if severe comorbid illness (euthyroid sick syndrome) is present.

Myxedema is life-threatening and must be considered in any patient with an altered level of consciousness and hypothermia. "Clinically suspected" cases should probably be treated in the appropriate clinical setting before laboratory confirmation. Our patient was successfully treated with intravenous levothyroxine and liothyronine followed by oral levothyroxine on the basis of a strong initial clinical suspicion of myxedema coma that laboratory data later confirmed.

The mortality rate has declined from 50% to 80% down to 15% to 50%, as cases are now diagnosed earlier and appropriate care instituted, preferably in intensive care units.