

Myxedema Coma In The Elderly

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Background: Myxedema coma in the elderly, although uncommon, is frequently overlooked and has a high mortality rate. Signs and symptoms are many and are often insidious. Nearly every organ system is involved. Prompt recognition and treatment are mandatory for a successful outcome.

Methods: A case study is presented. Using the key words "myxedema" with the word "aged," MEDLINE files were searched from 1989 to present. Articles dating before 1989 were accessed from the reference lists of the more recent articles.

Results and Conclusions: This review describes the signs and symptoms of myxedema coma in the elderly. Epidemiology and histopathology of the disorder are discussed. Prompt recognition and emergency medical treatment are essential for a successful outcome. Prevention requires screening of elderly patients at risk for hypothyroidism and assuring thyroid hormone replacement therapy. (J Am Board Fam Pract 1995; 8:376-83.)

Myxedema coma, the extreme expression of hypothyroidism, is a medical emergency requiring a high degree of clinical suspicion. The term *myxedema* was proposed by Ord in 1878 to describe the peculiar nonpitting swelling of skin in the hypothyroid adult and has been used interchangeably with hypothyroidism in the medical literature.¹ Although the actual incidence is unknown, myxedema coma is uncommon; only 200 cases were reported between 1953 and 1986.² The mortality rate in these patients is 50 percent or greater even with immediate thyroid hormone replacement therapy and supportive measures. Early recognition and intervention can be lifesaving.

Illustrative Case

A 90-year-old woman who had been residing in a nursing home for several years was brought in for consultation. The nursing staff and family reported gradually increasing lethargy, depression, and diminished mental alertness.

She had a history of cerebrovascular accidents, which precipitated her nursing home admission. The medical chart reflected persistent chronic hyponatremia unresponsive to fluid restriction. The patient had increasing pulmonary and peripheral edema as a result of congestive heart failure. Treatment with diuretics had worsened her

sodium depletion. A history of thyroidectomy for goiter in the remote past was discovered, and the patient had not received thyroid hormone replacement therapy. A family history was notable in that her son had a thyroid goiter.

During the physical examination the woman was obtunded and unable to communicate with the examiner. She weighed 72.7 kg, her temperature was 36.3°C, her pulse was regular at 80 beats per minute, respirations were 24/min, and her blood pressure was 178/94 mmHg. On appearance her face was swollen, especially about the eyes. Her mucous membranes were dry and the tongue was thickened. Neck masses were not found. Her skin was cool and doughy in consistency, and there was marked pitting edema of the lower extremities up to the knees. Lung examination demonstrated bilateral pulmonary edema with pleural effusions. The heart had a regular rate and rhythm with a grade II/VI systolic ejection murmur. Neurologically the patient was semicomatose. Deep tendon reflexes were diminished with a slowed response. Rectal examination found a fecal impaction.

Laboratory studies disclosed the following values: sodium 127 mEq/L, potassium 3.9 mEq/L, chloride 93 mEq/L, and carbon dioxide 25 mEq/L. Blood urea nitrogen (BUN) and serum creatinine were 17 mg/dL and 0.6 mg/dL, respectively. Serum osmolality was 250 mOsm/kg. Her fasting blood glucose was 128 mg/dL. The serum total protein was 5.8 g/dL, and serum albumin was 3.1 g/dL. A complete blood count showed a mild microcytic, normochromic anemia. A urinalysis was positive for pyuria and bacteriuria. Thyroid function studies showed a depressed

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thyroxine level of 3.0 $\mu\text{g}/\text{dL}$ and an elevated thyroid stimulating hormone (TSH) of 53 $\mu\text{U}/\text{mL}$. An adrenocorticotropic hormone (ACTH) level was normal at 34 pg/mL . A blood gas determination on 2 L of nasal cannula oxygen revealed acidosis with a pH of 7.24, pO_2 of 118 mmHg, pCO_2 of 145 mmHg, and a bicarbonate of 50.4 mEq/L. A chest radiograph showed marked cardiomegaly with bilateral pleural effusions. A two-dimension echocardiogram showed mild aortic stenosis and a dilated left ventricle with preserved function.

The patient was hospitalized for myxedema coma caused by untreated hypothyroidism with concurrent metabolic derangement, possible heart failure, and urinary tract infection. She received intravenous hydrocortisone 75 mg every 6 hours. An initial bolus of 400 mg of synthetic thyroxine was followed by 200 mg on day 2 and 100 mg daily thereafter. She received treatment of her heart failure with diuretics, supplemental oxygen and potassium, and digoxin. On day 5 she was switched to oral medications of prednisone 10 mg, levothyroxine 125 mg, digoxin 25 mg, and indapamide 2.5 mg. A follow-up chest radiograph showed resolution of the pulmonary congestion.

The patient returned to the nursing home on supplemental oxygen. During the next few months the patient had an improved level of alertness and was able to recognize family members. Her cardiac failure improved, and her metabolic problems stabilized.

Epidemiology

Myxedema coma occurs almost exclusively during or after the 6th decade with 80 percent of the cases occurring in women.^{3,4} More than 90 percent of cases have been reported to have occurred during winter months and are frequently associated with intercurrent illness or stressors (Table 1). Pneumonia or other infections and sedating drugs are common precipitants.⁴⁻⁶ About 50 percent of myxedema coma patients have lapsed into coma after admission to the hospital, probably as the result of stress caused by diagnostic and therapeutic interventions encountered during hospitalization.

Histopathology

The clinical manifestations of myxedema are induration and thickening of the skin, attributable

Table 1. Precipitating Causes of Myxedema Coma.

Cause	Type	
Infections	Pneumonia	
	Urinary tract infection	
	Influenza	
Drugs	Sedating	Narcotics
		Phenothiazines
		Tranquilizers and barbiturates
	Other central nervous system depressants	
	General anesthesia	
	Cardiac drugs	β -Blockers
Amiodarone		
Stressors	Surgery	
	Hospitalization	
	Burns	
	Trauma	
	Exposure to cold	

to the water-binding capacity of the acid glycosaminoglycans within the papillary and reticular layers.⁷ Other changes of the skin that contribute to edema in myxedema are increased capillary permeability, lymphatic obstruction, and perivascularitis. Acid glycosaminoglycans are also found in the tissues of the tongue, myocardium, striated muscle, and intestines.⁸ Thyroid hormone replacement treatment reduces hyaluronic acid concentrations in the skin, whereas the three other glycosaminoglycans remain unchanged.⁹ Muscle biopsy in severe myxedema reveals type II muscle fiber loss and atrophy, an increased number of mitochondria, and an accumulation of glycogen and lipids on the membranes. This effect is also somewhat reversible with treatment.¹⁰

Clinical Presentations

Because the patient is in a coma, the initial diagnosis is suggested by a history of clinical signs and symptoms of hypothyroidism and a history of thyroid surgery, high-dose external radiation of the neck, or discontinuation of thyroid hormone replacement therapy (Table 2).

In addition to knowing the symptoms preceding the onset of coma, physical findings will also aid the physician in making the diagnosis. The patient typically has periorbital swelling, ptosis, and a thickened tongue. Nonpitting edema of the

Table 2. Clinical Signs and Symptoms of Myxedema Coma.

Area	Sign or Symptom
Constitutional, general	Lethargy
	Weight gain or loss
	Weakness
	Sleep disturbance
Head and neck	Hearing impairment
	Obstructive sleep apnea
	Macroglossia
	Periorbital swelling
	Lid ptosis
Dermatologic	Hair loss
	Coarse, dry skin
	Pretibial myxedema
	Edema
Gastrointestinal	Fecal impaction
	Megacolon
Urologic	Bladder atony
	Urinary retention
Musculoskeletal	Muscle hypertrophy
Neurologic and psychiatric	Psychosis
	Restlessness
	Delirium
	Dementia
	Psychomotor retardation

lower extremities is the hallmark of myxedema; however, 40 percent of patients could have pitting as a result of heart, renal, or liver disease. Most hypothyroid patients are within 15 percent of their ideal body weight; the impression of being overweight might be due to puffiness of the face and extremities and the lack of weight loss with reduced oral intake. In the severely apathetic hypothyroid patient weight loss will occur.¹¹ Gross obesity is rare. Fine hair texture and nonscarring, diffuse alopecia can also be present.¹² Diminished eyebrows are a nonspecific finding and might be found in normal patients. Neck goiter is usually absent in the elderly hypothyroid patient, although a diffuse or nodular goiter can be present in 3.5 percent of patients.¹¹ A neck scar would be a clue to previous thyroidectomy and would be very helpful in making the diagnosis.

Abdominal findings include constipation, fecal impaction, abdominal distention, ascites, and a distended bladder caused by retention and atony.¹¹⁻¹³ Myxedema megacolon is a life-threatening condition. Intestinal mucopolysaccharides separate the muscle fibers of the intestine from the ganglia of the Auerbach plexus with resulting

atony. This serious condition can lead to visceral perforation. The resulting colonic ileus can be indistinguishable from mechanical obstruction.¹⁴ Barium enema shows localized transverse thickening of the colonic haustration.¹⁵ Myxedema megacolon appearing as pseudomembranous colitis and intestinal ischemia is rare.¹⁶ Hypotonia of the esophagus, stomach, duodenum, gallbladder, and small intestine can also occur.

The lowered metabolic state in myxedema coma patients results in bradycardia, slowed respiratory rate, hypothermia, and hypotension.¹⁷ Shivering is diminished or absent. Hypothermia, common in the aging population, can also be found with hypoglycemia and occasionally septicemia.¹⁸ A core temperature of less than 35.5°C occurs in about 80 percent of comatose patients. In fact, a normal temperature in a myxedema coma patient should be considered relative hyperthermia. Underlying infection in these patients is common and might be the precipitating factor leading to coma. Reduced immune defenses often obscure the signs of infection.

In the severe, chronic hypothyroid patient, the heart can be dilated and the myocardium atonic. Diminished heart sounds and breath sounds are usually found on examination. Infiltrative cardiomyopathy results in pericardial effusions in 30 to 80 percent of untreated patients.¹⁹ Infrequently cardiac tamponade will occur, even months after thyroid hormone replacement therapy, but eventually it will respond to treatment.²⁰ Pleural effusions also occur with or without congestive heart failure.^{21,22}

Metabolism and Physiology

Several metabolic derangements occur in myxedema coma and are important diagnostic and therapeutic considerations. Respiratory acidosis, hypoxia, and hypocapnia occur for several reasons (Table 3). Alveolar hypoventilation is caused by associated muscle weakness, coma, airway obstruction from edema and secretions, and an increased sensitivity to sedating drugs.²³ Further respiratory failure, hypercapnia, and hypoventilation result from central nervous system insensitivity to rising arterial blood carbon dioxide (CO₂).²⁴ Obstructive sleep apnea has been reported and complicates this problem.²⁵

A reduction in cardiac index also occurs by several mechanisms (Table 4).²³ Infiltrative cardio-

Table 3. Mechanisms of Respiratory Acidosis in Myxedema Coma.

Ventilatory muscle dysfunction
Myopathy
Coma
Upper airway obstruction
Secretions
Defective cough reflex
Sleep apnea
Diminished central nervous system sensitivity to carbon dioxide
Sensitivity to sedating drugs

myopathy and hypothermia depress myocardial contractility. Bradycardia, increased systemic vascular resistance, and eventual hypovolemia contribute to a reduced cardiac index. Because the patient's metabolic requirements and oxygen consumption are also reduced, a diminished cardiac index can remain adequate to meet the patient's metabolic needs.

Hyponatremia in the myxedema coma patient could be due entirely to hypothyroidism or could be accentuated by systemic illness. Less often hyponatremia is due to inappropriate antidiuretic hormone production or adrenal insufficiency. A decrease in free water clearance attributed to an increased release of antidiuretic hormone and to intrarenal abnormalities leading to decreased distal tubular delivery of hypotonic filtrate is the principal explanation of hyponatremia.^{26,27} A diminished urine output results from a decreased glomerular filtration rate and decreased renal blood flow and hypovolemia.

Hypoglycemia indicates the possibility of adrenal insufficiency that occurs in 5 to 10 percent of myxedema coma patients. Adrenal insufficiency is due to a sluggish pituitary-adrenal axis and is exacerbated by the increased metabolism of cortisol that occurs once thyroid hormone replacement therapy begins. Primary adrenal failure is uncommon, and when it occurs with Hashimoto thyroiditis, it is known as Schmidt syndrome.

Serum calcium levels are usually normal or slightly decreased. Occasionally hypercalcemia and hypophosphatemia result from diminished urinary excretion of calcium in thyroid-deficient patients.^{28,29}

Laboratory Findings

Typically a low serum thyroxine (T₄) and possibly triiodothyronine (T₃) are found in the severely

hypothyroid patient. Thyroid-stimulating hormone (TSH) is the most sensitive test in determining hypothyroidism and is the first laboratory abnormality seen in myxedema coma patients. In secondary or tertiary hypothyroidism caused by pituitary or hypothalamic dysfunction, respectively, TSH will not be elevated. The newer high-sensitivity TSH test is helpful in diagnosing hyperthyroidism, but levels would also be elevated in cases of hypothyroidism.

The diagnosis of secondary or tertiary hypothyroidism is critical from a mortality and management standpoint. Secondary hypothyroidism results from pituitary failure. An isolated pituitary trophic hormone defect is rare, and most cases of secondary hypothyroidism result from pituitary tumors or postpartum pituitary necrosis. Tertiary, or hypothalamic, hypothyroidism is usually due to trauma, tumor, or irradiation. Although idiopathic cases exist, hypothalamic insufficiency is uncommon. In either case of secondary or tertiary hypothyroidism the TSH and T₄ levels are low, as are the gonadotropins in the postmenopausal woman and serum cortisol in both female and male patients. A thyroid replacement hormone administration assay would be useful in that no detectable rise in base-line serum TSH would occur.

Thyroid microsomal and thyroglobulin antibodies are frequently elevated in cases of primary hypothyroidism from autoimmune or idiopathic causes. Knowing the antibody levels can be helpful in the diagnosis, because these antibodies fall dramatically after treatment with thyroid hormone replacement therapy. This response might reflect reduced antigen availability to the immune system resulting from a decreased stimulation of thyroid tissue by TSH.³⁰ The degree of abnormality of the thyroid hormone does not correlate with the level of consciousness in these patients.³¹

Because myxedema coma has profound effects on the cardiovascular system, many cardiac

Table 4. Mechanism of Reduction on Cardiac Index in Myxedema Coma.

Depressed myocardial contractility
Cardiomyopathy
Hypothermia
Bradycardia
Increased systemic vascular resistance
Hypovolemia

parameters are found to be abnormal. Cardiac isoenzyme profiles are elevated, suggesting myocardial infarction even in the absence of ischemia.³² This finding can be misleading, because the myxedema coma patient is at risk for myocardial compromise and just such a complication.^{33,34} In addition to elevations in lactic dehydrogenase and aspartate aminotransferase, creatinine phosphokinase (CPK) activity is usually increased. Although CPK myocardial bands can be present, most of the CPK isoenzyme is of muscle origin. This abnormality is thought to be due to increases in membrane permeability in muscle rather than muscle destruction.³⁵ These enzyme abnormalities persist until thyroid hormone replacement therapy has occurred.

Electrocardiographic abnormalities are found in myxedema coma with or without pericardial effusions. Common findings include sinus bradycardia, small voltage complexes, T wave inversions and nonspecific T wave flattening. Type one atrioventricular (AV) block and prolonged QT intervals are also seen.²³ These findings, with the exception of inverted T waves, resolve with treatment, which suggests possible permanent structural changes have occurred.³⁶ Reversible AV block is rare.³⁷ ST wave changes are not characteristic in myxedema coma. T wave flattening or inversion might also be an indication of underlying coronary artery disease and cardiac ischemia.

Echocardiographic studies are useful in detecting pericardial effusions that might be undetectable in a chest radiograph. The incidence of pericardial effusions is 30 to 78 percent in various studies.³⁶ Asymmetric septal hypertrophy or idiopathic hypertrophic subaortic stenosis has been reported as being secondary to hypothyroidism. These findings can be reversible with thyroid hormone replacement therapy.³⁸

Room air blood gas measurements are necessary and reflect respiratory acidosis. Electrolyte disturbance includes hyponatremia, hypokalemia, and possibly hypochloremia. Elevated creatinine levels are not uncommon. Hypoglycemia suggests a pituitary, hypothalamic, or adrenal defect. Low serum glucose levels can persist several weeks after treatment. Elevated C peptide levels can be due to hypometabolism.³⁹ Serum lactate is usually normal. Serum cholesterol and triglycerides are elevated and of little clinical importance, though lipid levels can be depressed in the pro-

foundly ill patient. Carcinoembryonic levels are elevated and nonspecific, and there can be a mild anemia of the normocytic, normochromic type. Microcytosis is rare. The white cell count and platelets are usually normal.

Thrombocytopenia has been reported in hypothermia secondary to the sequestration of platelets in the liver and spleen. Ten percent of hypothyroid patients also have pernicious anemia, possibly as the result of an immune dysfunction.⁴⁰

There are no electroencephalographic characteristics that are pathognomonic of myxedema coma. Slowing of the alpha rhythm and diminution of the reaction to light stimulation are present but nonspecific. Hypothermia results in a pronounced lowering of the amplitude of background activity. Cerebrospinal fluid in myxedema coma patients has elevated protein levels of 40 to 90 percent beyond normal and can be greater than 100 mg/dL. Elevated cerebrospinal fluid and serum gamma globulin levels have been reported. The opening pressure upon lumbar puncture is elevated.⁴¹ Electromyographic and nerve conduction abnormalities exist and are consistent with the commonly found polyneuropathy with a demyelinating component.⁴¹

Treatment

Treatment of myxedema coma must be initiated upon suspicion of the condition before confirmatory laboratory findings. Management consists of supportive therapy, hormone replacement, and treatment of underlying and concurrent illness.

The myxedema coma patient should be admitted to an intensive care unit or similar telemetry floor for close and continuous cardiac monitoring. Reestablishment of the airway could be necessary in cases of extreme hypoventilation, hypercapnia, and hypoxia. Intubation of the airway should be approached with caution. The delicate, swollen laryngeal mucosa is easily damaged by traumatic or prolonged intubation. Hypothyroid patients are more difficult to wean from ventilatory assistance because of carbon dioxide retention.⁴²

Administration of intravenous fluids is a necessary treatment of hypovolemia and hypotension and to correct for electrolyte disturbance. Careful fluid status monitoring is important because of the compromised cardiovascular state, and a Swan-Ganz catheter can be useful to monitor this

situation. Avoid hemodynamic overcorrection in this low metabolic state. A combination of slow saline infusion and water restriction is the treatment of choice.

Inotropic drugs, such as digoxin, might be needed in the hemodynamically unstable patient. These drugs must be prescribed with extreme caution because they are synergistic with thyroid replacement, and adverse reactions, such as arrhythmias, are common. If a pressor agent is necessary, dopamine is preferred to norepinephrine to maintain coronary, mesenteric, and renal perfusion.

The method of thyroid hormone replacement therapy in the myxedema coma patient has been a focus of controversy. Because this condition is uncommon, controlled studies on the method of replacement therapy do not exist. In early reported cases patients received low-dose thyroid replacement, but the mortality in these cases exceeded 80 percent. In the mid-1960s, Holvey, et al.⁴³ reported several cases successfully treated with high-dose intravenous thyroxine replacement. L-Thyroxine should be administered intravenously at a dose of 250 to 500 mg for a 30- to 60-second period. A dose can be administered 12 hours later if the body temperature and sensorium are not improved. The intravenous route results in high peaks of plasma T_4 . Peripheral conversion of T_4 to T_3 allows gradual T_3 delivery to organ systems even if only L-thyroxine is used. Although administration of T_3 is more potent, it is associated with greater mortality, whereas T_4 is easier to administer and less stressful to critically ill patients.

Once the patient is capable of taking oral medications, a maintenance dose can be administered daily. Oral absorption of L-thyroxine is variable, but a clinical response does occur, even in cases of myxedema ileus.⁴⁴ Elderly patients require T_4 dosing in a range of 100 to 170 mg daily. This maintenance dose has been found to be lower than that needed for younger patients because the T_4 degradation rate declines with aging.^{45,46} Serum T_4 , free thyroxine index, and T_3 can be transiently elevated early in the course of replacement therapy. Within the first 6 weeks of replacement therapy, these levels might even be within the thyrotoxic range as a result of the decreased metabolic clearance rate of the absorbed hormone. These levels then stabilize 4 to 8 months later. As a result the serum T_4 and T_3 levels dur-

ing the first 6 months of therapy do not reflect the optimal dose of T_4 replacement on a long-term basis.⁴⁷

The lowered metabolic state and possible secondary or tertiary hypothyroidism complicate medical management. All stuporous patients with either hypotension or hyponatremia require stress level corticosteroid replacement. Hydrocortisone, 200 to 300 mg, should be given in daily divided doses for 3 to 7 days. In the confirmed absence of secondary or tertiary hypothyroidism, the corticosteroids can be tapered rapidly. Such therapy causes no harm to the primary hypothyroid patient and can be lifesaving to the others.

Concurrent illness is frequently present and acts as a precipitant in the comatose patient. Signs of underlying infection, such as fever and leukocytosis, are commonly masked. Pneumonia, urinary tract infection, and bacteremia are common and should be sought and treated empirically. Urinalysis, cultures, and chest radiograph should be obtained early in the workup of the patient. Myocardial infarction, congestive heart failure, and cerebrovascular accident are common in such patients and need to be treated accordingly.

Adverse Reactions to Treatment

Determinants of fatal outcome in myxedema coma patients include old age and high serum T_3 levels.⁴⁸ Treatment of the comatose patient results in immediate cardiovascular changes. Increases occur in oxygen consumption, oxygen delivery, cardiac output, heart rate, and ventricular response.⁴⁹ Overly aggressive treatment of the comatose patient precipitates tissue hypoxia and possible myocardial infarction.

Actual rewarming equipment is contraindicated in the hypothermic patient, who will respond to thyroid hormone replacement therapy alone. Active rewarming causes vasodilatation and refractory hypotension and can be fatal. Failure to address adrenal insufficiency will likewise result in cardiovascular collapse. Delayed respiratory failure during treatment of a comatose patient has been reported.⁵⁰

Prevention

Prevention is the greatest treatment for myxedema coma and its complications. Screening elderly women using a serum TSH measurement has

been proposed.⁵¹ Thyroid studies should be obtained and documented in all symptomatic elderly patients and before elective surgery. Known hypothyroid patients should be questioned about compliance with replacement therapy, and the adequacy of their treatment should be periodically monitored.

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