

NOTE

A case of myxedema coma caused by isolated thyrotropin stimulating hormone deficiency and Hashimoto's thyroiditis

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Abstract. Myxedema coma (MC) is a rare, but often fatal endocrine emergency. The majority of cases that occur in elderly women with long-standing primary hypothyroidism are caused by particular triggers. Conversely, MC of central origin is extremely rare. Here, we report a case of MC with both central and primary origins. A 56-year-old woman was transferred to our hospital due to loss of consciousness; a chest x-ray demonstrated severe cardiomegaly. Low body temperature, bradycardia, and pericardial effusion suggested the presence of hypothyroidism. Endocrinological examination revealed undetectable levels of serum free thyroxine (T_4) and free triiodothyronine (T_3), whereas serum thyroid-stimulating hormone (TSH) levels were not elevated. The woman's serum anti-thyroid peroxidase antibody and anti-thyroglobulin antibody tests were positive, indicating that she had Hashimoto's thyroiditis. Provocative tests to the anterior pituitary revealed that she had TSH and growth hormone (GH) deficiency; however, GH levels were restored after supplementation with levothyroxine for 5 months. This was not only a rare case of MC with TSH deficiency and Hashimoto's thyroiditis; the patient also developed severe osteoporosis and possessed transient elevated levels of serum carcinoembryonic antigen (CEA). This atypical case may suggest the role of anterior pituitary hormone deficiencies, as well as hypothyroidism, in the regulation of bone metabolism.

Key words: Myxedema, Secondary hypothyroidism, Hashimoto's thyroiditis, Osteoporosis

MYXEDEMA coma (MC) is a rare but extremely severe presentation of profound hypothyroidism that is associated with high mortality [1, 2]. The incidence of this condition in Europe is reported to be 0.22 per 1, 000, 000 cases per year [3]; the prevalence rate in our country is not known. This rare condition is most often observed in elderly women who have long-standing hypothyroidism, and is precipitated by a secondary insult such as exposure to cold, infection, drugs such as sedative-hypnotics, and associated systemic diseases [4-6]. Such cases are predominantly based on a primary thyroid disorder such as Hashimoto's thyroiditis. Much more rarely, however, the underlying cause in approximately 5% of myxedema cases is hypothalamic or pituitary disease, where the patient usually lacks multiple anterior pituitary hormones, including thy-

roid-stimulating hormones (TSH) [6]. In this report, we describe a patient with a rare condition who developed MC due to both central and primary origin, i.e., TSH deficiency (TSHD) and Hashimoto's thyroiditis. We also found it noteworthy that she had severe osteoporosis and an elevated serum carcinoembryonic antigen (CEA) level as well as massive amounts of pericardial effusion at the time.

Subject and Methods

Case report

A 56-year-old woman with loss of consciousness was admitted to a nearby hospital. Hormone evaluation revealed undetectable levels of serum free thyroxine (T_4) and free triiodothyronine (T_3), and she was transferred to our hospital for further evaluation and treatment. Her medical history, including that for thyroid dysfunction, heart disease, or serum cholesterol level was unclear since she had not seen a doctor for medical checkup. She experienced uneventful deliveries twice and had regular menstruation until her meno-

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Table 1 Laboratory data on admission

Complete Blood Count		Endocrinology	
White blood cell	5000 / μ L	ACTH	25.1 pg/mL
Red blood cell	342 $\times 10^4$ / μ L	Cortisol	21.0 μ g/dL
Hemoglobin	11.4 g/dL	TSH	4.10 μ U/mL
Hematocrit	34.6 %	Free T ₄	<0.40 ng/dL
Platelet	10.2 $\times 10^4$ / μ L	Free T ₃	<1.00 pg/mL
Blood Chemistry		GH	0.31 ng/mL
Total protein	6.5 g/dL	IGF-I	25 ng/mL
Albumin	3.1 g/dL	PRL	6.13 ng/mL
Aspartate aminotransferase	57 IU/L	LH	2.73 mIU/mL
Alanine aminotransferase	27 IU/L	FSH	36.15 mIU/mL
Lactate dehydrogenase	567 IU/L	Estradiol	<10 pg/mL
Alkaline phosphatase	286 IU/L	Anti-TPOAb	67 IU/L
γ -glutamyltransferase	22 IU/L	Anti-TgAb	115 IU/L
Total bilirubin	1.5 mg/dL	Bone ALP	56.9 IU/L
Amylase	138 IU/L	Urine-NTx	229.9 nmolBCE/L
Creatinine kinase	1408 IU/L	Immunology	
Creatinine kinase-MB isozyme	97 IU/L	ANA	80 fold
Blood urea nitrogen	21.7 mg/dL	Anti-pituitary Ab	(-)
Creatinine	0.40 mg/dL	Anti-Pit1 Ab	(-)
Uric acid	2.8 mg/dL	Anti-GAD Ab	(-)
C-reactive protein	0.45 mg/dL	Arterial Blood Gas Analysis (in room air)	
Sodium	142 mEq/L	pH	7.426
Potassium	2.2 mEq/L	pCO ₂	80.0 Torr
Chloride	90 mEq/L	pO ₂	51.2 Torr
Calcium	8.2 mg/dL	HCO ₃	36.8 mmol/L
Phosphorus	1.8 mg/dL	BE	11.9 mmol/L
Total-Cholesterol	173 mg/dL	Abbreviations: Ab, antibody; ANA, antinuclear antibody; pCO ₂ , partial pressure of carbon dioxide; pO ₂ , partial pressure of oxygen; HCO ₃ , bicarbonate; BE, base excess	
HDL-Cholesterol	81 mg/dL		
Triglyceride	112 mg/dL		
Fasting serum glucose	114 mg/dL		
Hemoglobin A1c	5.8 %		
CEA	16.3 ng/mL		

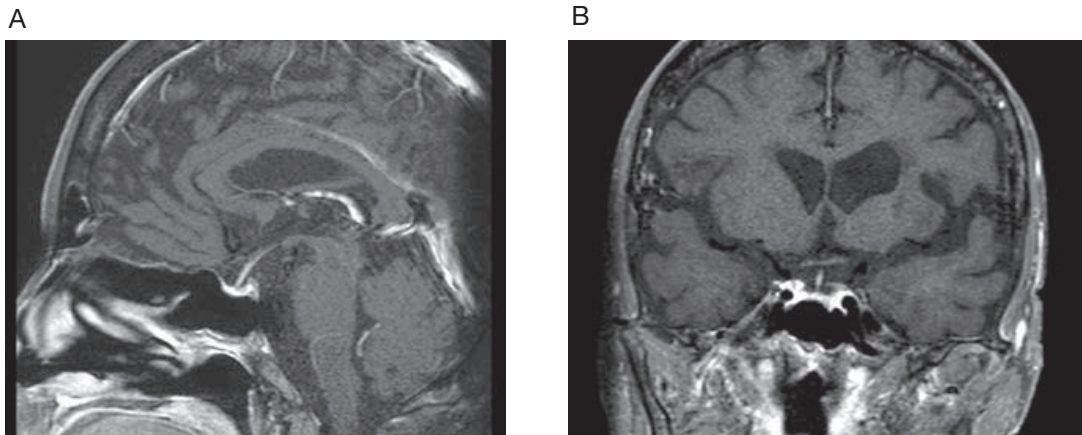
pause at the age of 48-year-old. She realized her hair loss when she was 50 year-old and felt general malaise 1 year before her admission.

The patient was 139 cm tall and weighed 42 kg, and was disoriented on admission. Her conscious level assessed by Glasgow Coma Scale was E₃V₃M₅. Her blood pressure was 140/80 mmHg, body temperature was 35.1°C, pulse was 45 beats per minute with atrial fibrillation, and oxygen saturation was 88% without administration of supplemental oxygen. Physical examination revealed mild facial edema and sparse hair on her head. Her thyroid gland was not palpable, breath sounds in the lower chest were diminished and heart beat were widely spaced with an irregular rhythm. The abdomen was soft and flat, and the patient had dry skin with pretibial, non-pitting edema.

The results of the laboratory examination are displayed in Table 1. Peripheral blood tests detected normal levels of serum sodium, decreased levels of serum potassium, and elevated levels of serum creatinine kinase. Her serum cholesterol level was normal, and serum CEA level was elevated at 16.3 ng/dL. Hormone evaluation demonstrated decreased serum growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels. Her serum prolactin (PRL) and luteinizing hormone (LH)/ follicle-stimulating hormone (FSH) level was relatively decreased irrespective of her hypothyroid and postmenopausal state, respectively. A thyroid function test reported undetectable levels of both free T₄ (<0.4 ng/dL) and free T₃ (<1.0 pg/mL), but normal TSH levels of 4.1 μ U/mL. Measurement of thyroid antibodies showed elevated thyroid peroxidase

Table 2 CRH/TRH/LHRH/GHRP-2 tests

Time (min)	0	15	30	45	60	90	120
GH (ng/mL)	0.31	4.90	3.58	2.22	1.26	-	-
PRL (ng/mL)	5.10	-	17.69	-	10.90	8.38	7.43
TSH (μ U/mL)	1.484	-	3.251	-	3.171	2.559	2.230
ACTH (pg/mL)	25.1	-	204	-	150	94.3	94.7
Cortisol (μ g/dL)	21.0	-	29.9	-	31.9	34.9	31.8
LH (mIU/mL)	2.60	-	7.08	-	10.66	12.40	14.25
FSH (mIU/mL)	14.97	-	17.83	-	20.80	25.81	28.23

**Fig. 1** Sagittal (A) and coronal (B) section of T1-weighted MR image of the pituitary gland demonstrating an atrophic gland without tumor lesions.**Fig. 2** Chest x-ray of the patient on admission showing diffuse cardiomegaly.

(TPO) antibody and thyroglobulin (Tg) antibody titers of 67 IU/mL and 115 IU/mL, respectively, suggesting the presence of Hashimoto's thyroiditis. As serum TSH levels were not extremely elevated irrespective of undetectable levels of free T_4 and free T_3 , we diagnosed her with central, rather than primary, hypothyroidism before evaluating pituitary function as well. As shown in Table 2, TSH and GH levels responded

poorly to intravenous administration of thyrotropin-releasing hormone (TRH) and GH-releasing peptide-2 (GHRP-2), respectively, whereas adrenocorticotropin (ACTH) levels responded well to intravenous administration of corticotrophin-releasing hormone (CRH). There was a delayed response of LH and FSH levels to intravenous administration of LH-releasing hormone (LHRH). Magnetic resonance imaging (MRI) of the pituitary gland revealed an empty sella and an atrophied pituitary gland (Fig. 1). These data suggested the possible presence of TSH and GH deficiency. Taken together with the positive results for anti-TPO and anti-Tg antibody tests, we concluded that the patient's severe hypothyroidism was caused by both TSHD and Hashimoto's thyroiditis, and autoimmune mechanisms might have accounted for the patient's pathogenesis. We detected positive anti-nuclear antibody levels but failed to detect anti-pituitary or anti-Pit1 antibodies, respectively.

The patient's chest x-ray demonstrated severe cardiomegaly and pleural effusion (Fig. 2). An electrocardiogram and echocardiogram revealed atrial fibrillation and massive amounts of pericardial effusion

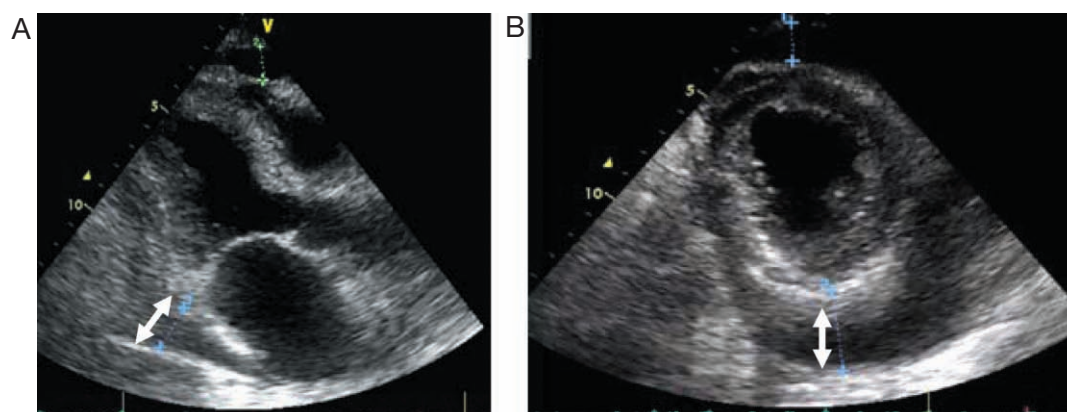


Fig. 3 Echocardiography with parasternal long axis (A) and apical views (B) revealing massive amounts of pericardial effusion (arrow) without hemodynamic significance.

Table 3 GHRP-2 test after levothyroxine treatment for 5 months

Time (min)	0	15	30	45	60
GH (ng/mL)	0.97	22.7	15.3	10.1	6.41

(Fig. 3), respectively. However, the pericardial effusion did not affect the patient's hemodynamic status. An ultrasonograph of the thyroid gland revealed an atrophied gland with heterogeneous echogenicity. The bone mineral density (BMD) of the patient's lumbar spine was remarkably diminished, with a value of -4.8 standard deviations as compared to a young adult's mean. Serum markers for bone formation (bone alkaline phosphatase) and absorption (urinary cross-linked N-telopeptides of type I collagen: NTx) were both elevated.

Clinical course

Due to the possibility of secondary adrenal insufficiency, we initiated adrenocortical hormone replacement therapy with an intravenous infusion of 100 mg of hydrocortisone every 8 hours, followed by oral administration of levothyroxine at an initial dose of 200 µg daily for 2 days. As a result, the patient's awareness level gradually improved. Following this, dosages for hydrocortisone and levothyroxine were reduced to 20 mg and 50 µg, respectively, with oral administration of hydrocortisone replacing that of the earlier intravenous infusion. After hormone examination determined that pituitary-adrenal function was normal, hydrocortisone replacement was discontinued and the dosage of levothyroxine gradually increased until a daily maintenance dose of 150 µg was achieved. Moreover, warfarin and furosemide was administered orally to remedy

the atrial fibrillation and cardiac and/or pleural effusion, respectively. Bisphosphonate was administered prophylactically due to the patient's severe osteoporosis. As shown in Table 3, GH levels eventually recovered 5 months after admission with a reduction in pericardial effusion and a normalization of serum CEA levels at 4.1 ng/mL. Her serum free T₄ and TSH levels were 1.45 ng/dL and 0.373 µU/mL, respectively, after the replacement of levothyroxine for 5 months. The basal levels of serum PRL, LH and FSH were restored to the value of 19.38 ng/mL, 21.77 mIU/mL and 58.54 mIU/mL, respectively. Our final diagnosis for the patient was isolated TSHD (ITSHD) with Hashimoto's thyroiditis.

Discussion

In this report, we describe the case of a patient falling into a myxedema coma caused by ITSHD with Hashimoto's thyroiditis. Our case displayed several interesting characteristics, which are described as follows.

First, ITSHD resulting in myxedema is a rare etiology. A previously reported case of myxedema heart disease caused by ITSHD [7] was characterized by an absence of the common signs and symptoms of hypothyroidism. In our case, however, typical signs of severe hypothyroidism, such as cardiomegaly with pericardial effusion, facial and non-pitting edema, and

an elevation of serum creatinine kinase levels were present, whereas hypercholesterolemia was absent. In addition, our patient suffered not only from TSHD, but Hashimoto's thyroiditis as well. Another case had reported myxedema coma with both central and primary origins [8], although that patient developed multiple pituitary hormone deficiency, including TSHD, due to Sheehan's syndrome. Although the etiology of ITSHD remains unknown, pathogenesis may possibly be due to autoimmune mechanisms since ITSHD was often accompanied by type 1 diabetes mellitus [9] and the presence of anti-pituitary antibodies [10], or it occurred during the postpartum period [11]. Our patient presented with Hashimoto's thyroiditis as well the absence of anti-glutamic acid dehydrogenase (GAD) or anti-pituitary antibodies. Very recently, we reported a new syndrome showing acquired GH, PRL, and TSH deficiencies, with an anti-Pit1 antibody as the probable cause [12]. Anti-Pit1 antibodies were absent in the case we describe, although the patient demonstrated a relatively low response in GH and PRL level recovery after the intravenous administration of GHRP-2 and TRH, respectively (Table 2).

Second, the patient's hypothyroidism was associated with a remarkable elevation in serum CEA levels, which rapidly decreased after the hypothyroidism was treated. Positive CEA levels have been observed with high frequency in hypothyroid patients with Hashimoto's thyroiditis [13], in agreement with our observation. Although the mechanism causing high serum CEA levels in patients with hypothyroidism remains unknown, it may be caused by decreased degradation of CEA.

Third, our patient developed severe osteoporosis. It remains unknown how is the BMD in patients with central hypothyroidism probably due to a rare disease. There are several possible explanations in terms of her severe osteoporosis. One explanation may be due to the mild gonadotropin insufficiency. However, our patient experienced deliveries twice and had regu-

lar menstruation until the age of 48 year-old, suggesting that hypogonadism is unlikely the main cause of her severe osteoporosis. Alternative explanation may be long-standing GH-IGF-I deficiency associated with hypothyroidism. It is established that GH-IGF-I axis is crucial factor for the maintenance of normal bone mass [14]. However, serum markers for bone remodeling are usually decreased in patients with GH deficiency [15] whereas our patient showed increased turnover of bone metabolism. Otherwise, immobility can also negatively affect a patient's BMD [16]. It is also possible that TSH deficiency as well as hypothyroidism might affect the reduced BMD in our patient. A previous experimental study that utilized TSH receptor disrupted mice found that TSH rather than thyroid hormones per se regulate skeletal remodeling [17]. Heterozygous mice with 50% reduction in TSH receptor expression (TSHR+/-) developed severe osteoporosis with high rates of skeletal remodeling even though they were in a euthyroid state. In addition, dietary thyroid extract supplementation in TSHR-/- mice aimed at normalizing serum thyroid hormone levels failed to reverse the low bone mass density, suggesting the direct effect of TSH rather than T₃ or T₄ on bone remodeling [17]. Taken together, the extremely low BMD and increased bone remodeling markers in our patient may have been caused by several hormonal factors including GH, TSH, and gonadotropin deficiencies in association with severe hypothyroidism.

In conclusion, we report a rare case of myxedema coma caused by TSHD and Hashimoto's thyroiditis. The patient developed abundant pericardial effusion, elevated levels of serum CEA, and severe osteoporosis with high turnover in bone remodeling.

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