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A Case of Subclinical Hypothyroidism Developing Marked Pleural Effusions and Peripheral Edema with Elevated Vascular Endothelial Growth Factor

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Abstract. A 69-year-old woman was admitted for the treatment of marked pleural effusions and peripheral edema. Analytical studies of the pleural effusion revealed exudates. Culture for bacterial organisms and tuberculosis were negative, and cytology was normal. She had a mediastinal tumor at the age of 61 and regular follow-up showed no evidence of malignancy. She underwent the mediastinal tumor resection, because we thought this was the cause of her symptoms. However, her clinical symptoms persisted after surgery. Next, we noticed subclinical hypothyroidism, in which serum TSH level was elevated with concomitant normal thyroid hormone levels. In addition, serum vascular endothelial growth factor (VEGF) levels, which have been reported to be related to the pathophysiology of the extravascular volume overload, were elevated. Although her TSH level was slightly elevated (15.4 μU/ml), we started thyroid hormone replacement therapy. This therapy gradually ameliorated her clinical manifestation and abnormal laboratory data, including elevated VEGF levels. These observations indicate that even subclinical hypothyroidism may cause severe clinical manifestations. Furthermore, elevated VEGF may be a contributing factor in the pathogenesis of extravascular volume overload in hypothyroid patients.

Key words: Primary myxedema, Hypothyroidism, VEGF, Estradiol, Pleural effusion

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SUBCLINICAL hypothyroidism is defined as a condition with an elevated TSH and normal free T_4 (FT_4), despite the confusing nomenclature [1–3]. The overall prevalence has been reported to range from 4%–10% in large general population screening surveys and from 7%–26% in studies of the elderly [1]. The condition may be associated with cardiac dysfunction, increased risk for the development of atherosclerosis, elevation in total and low-density lipoprotein (LDL) cholesterol, systemic hypothyroid symptoms, neuropsychiatric symptoms, and progression to overt, symptomatic hypothyroidism [3]. The measurement of TSH is the most sensitive test for early diagnosis of primary hypothyroidism; however, TSH may be a poor measure for estimating the clinical and metabolic severity of overt hypothyroidism [4].

Effusions in serous body cavities, including peritoneal, pleural and pericardial, are frequently recognized in hypothyroidism [5, 6]. Although increased capillary permeability with leakage of plasma proteins was reported in hypothyroid patients [7], the mechanism by which these effusions develop is not well understood. Vascular endothelial growth factor (VEGF) is an angiogenic and mitogenic substance that seems to be active in vascular endothelial cells [8–10] and plays an important role in tumor growth and in the metastatic

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process [11]. VEGF is also known as a vascular permeability factor and induces a rapid and reversible increase in vascular permeability [12, 13]. Recently, an association of edema with increased VEGF levels has been demonstrated in many pathological conditions, such as POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome [14], ovarian hyperstimulation syndrome [15], preeclampsia [16], and diabetic patients with troglitazone treatment [17].

Here we report a case of primary hypothyroidism with severe clinical manifestations, though the biochemical thyroid function showed subclinical hypothyroidism. She had marked pleural effusions and peripheral edema, with elevated VEGF.

Case Report

A 69-year-old woman suffered from cough and dyspnea in June 2000 and bilateral pleural effusion was observed. Her past medical history included the following conditions. At 37 years of age she underwent a total hysterectomy for rupture of the uterus during labor. She had no history of estrogen treatment. At the age of 50, she developed leg edema; however, she ignored the condition. At 61, she had a mediastinal tumor and regular follow-up showed no evidence of malignancy.

She was hospitalized for the treatment of pleural effusions in thoracic surgery in our hospital in July 2000. Chest radiography demonstrated massive bilateral pleural effusions (Fig. 1A) and echocardiography showed pericardial effusions. Analytical studies of the pleural effusion revealed exudates with protein 3.6 g/dL and cell count of 400/mm^3. Lymphocytes were predominant (90%). Culture for bacterial organisms and tuberculosis were negative and cytology was normal. F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed a high-uptake lesion, which coincided with the anterior mediastinal tumor but no other abnormal uptake could be found. In August, she underwent both mediastinal tumor and pericardium resection. The pathological report of the surgical specimen was consistent with a benign thymoma of the noninvasive type. Her clinical symptoms persisted after surgery and it was noticed that this was not the cause of her symptoms.

After consultation with our peers, the possibility of hypothyroidism as a cause of her symptoms was considered. On physical examination, she had anasarca with pretibial pitting edema on her legs (Fig. 2A). Laboratory data showed mild decreased total protein and albumin levels (Table 1). Total cholesterol (T-Cho) and creatine kinase (CK) levels were within normal limit. Her thyroid function revealed subclinical hypothyroidism, such as slightly elevated TSH, and both free T_3 (FT_3) and FT_4 within normal range (Table 2). FT_3 and FT_4 were measured by immunoradiometric assays (Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Antithyroid peroxidase antibodies, antithyroglobulin antibodies and anti-TSH receptor antibodies were all negative. Thyroid ultrasound examination demonstrated an atrophic thyroid gland, with multiple

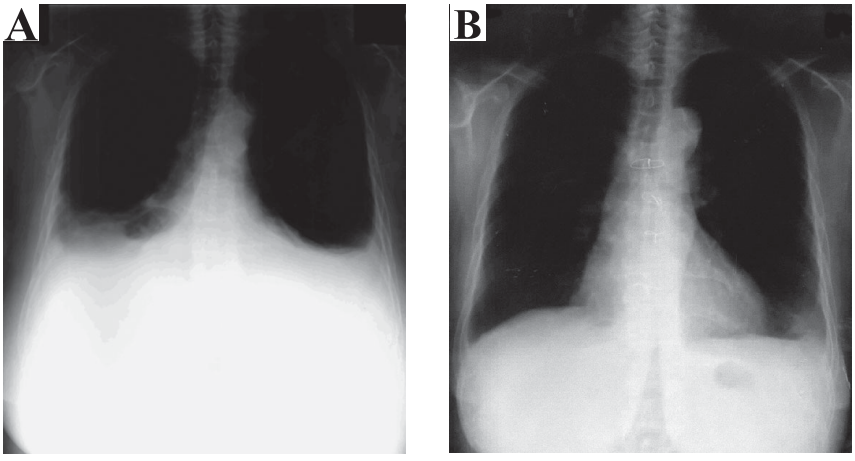

Fig. 1. Posteroanterior chest roentgenogram. A, in August 2000, demonstrating massive bilateral pleural effusions. B, in April 2001, demonstrating resolution of pleural effusions.

cysts in the thyroid. ^{99m}Tc pertechnetate thyroid scintigraphy showed a normal thyroid shape with even trapping and a normal uptake ratio [2.5% (normal range, 0.4–3.0%)]. Another endocrinological examination is shown in Table 2. Serum LH and FSH levels were 0.83 mIU/mL and 10.6 mIU/mL, with estradiol (E2) of 55 pg/mL.

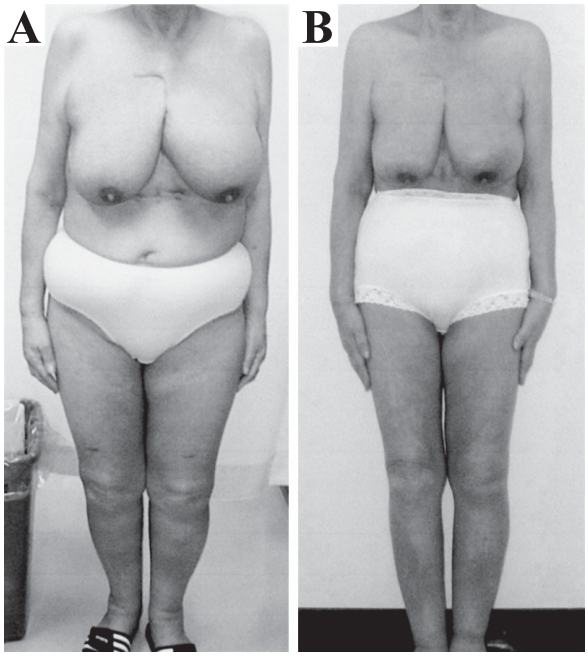

Fig. 2. A, Patient presented with marked peripheral edema in September 2000. B, Peripheral edema was improved after thyroid hormone replacement therapy in March 2001.

Initially, we suspected POEMS syndrome because she had marked pleural effusions and peripheral edema, even though her thyroid function showed a normal FT_4 and slightly elevated TSH. Furthermore, she had elevated E2 in spite of being postmenopausal. To evaluate polyneuropathy, motor nerve conduction velocity was performed, but was normal in both lower extremities. Abdominal computerized tomography scan showed a slightly enlarged liver, but neither splenomegaly nor apparent tumor lesion was found. Though serum IgG level was increased to 2185.7 mg/dL (normal range, 788.0–1841.0 mg/dL), serum immunoelectrophoresis did not reveal the possibility of IgG monoclonal protein, and bone marrow aspiration specimen showed no abnormality. Serum VEGF and interleukin-6 (IL-6) levels, which have been reported to increase in POEMS syndrome, were increased to 2289.9 pg/mL (normal range, 62.0–707.0 pg/mL) and 7.3 pg/mL (normal range, <4.0 pg/mL), respectively.

Clinical course of the patient

The patient did not have evidence of polyneuropathy, which was observed in 100% of POEMS syndrome [18]. In view of this, POEMS syndrome was ruled out. Though there was a slight elevation in TSH level, we started her on thyroid hormone replacement therapy. Levothyroxine sodium (T_4) was used at a dose of 25 μg/day from September and then gradually in-

Table 1. Laboratory data

Blood cell count		Normal range	Blood chemistry		Normal range
WBC	12000/μl	2700–8500	AST	22 IU/l	13–33
RBC	352 × 10^4/μl	319–494	ALT	11 IU/l	6.0–27.0
Hb	11.5 g/dl	10.2–14.9	ALP	238 IU/l	115–359
PLT	66.2 × 10^4/μl	11.0–34.7	TP	6.1 g/dl	6.3–8.1
			Alb	3.0 g/dl	3.9–5.1
			T-Cho	161 mg/dl	140–220
			Triglyceride	194 mg/dl	34–173
Urine			CPK	36 IU/l	35–141
Protein	(–)		BUN	10 mg/dl	8.0–22.0
Glucose	(–)		CRE	0.7 mg/dl	0.4–0.8
Ketone	(–)		Na	132 mEq/l	136–144
O.B.	(–)		K	3.5 mEq/l	3.6–4.8
			Cl	90 mEq/l	99–109
			Glu	107 mg/dl	78–110
			HbA1c	5.0%	4.8–5.8
			CRP	0.8 mg/dl	<0.2

Table 2. Endocrinological examination

	Reference interval			Reference interval	
TSH	15.4 μU/ml	0.41–4.0	LH	0.83 mIU/ml	4.2–79.6
FT_3	2.97 pg/ml	2.0–4.9	FSH	10.6 mIU/ml	12.6–235.7
FT_4	1.16 ng/dl	0.82–1.63	Estradiol	55 pg/ml	<16
TPOAb	<0.3 U/ml	<0.3	Testosterone	0.27 ng/ml	0.13–0.69
TgAb	<0.3 U/ml	<0.3	17α-OHP	0.2 ng/ml	0.1–3
TRAb	7.9%	<15	DHEA-S	774 ng/ml	50–1000
ACTH	11.9 pg/ml	7–56		Urinary hormone excretion	
Cortisol	10.2 μg/dl	5.0–15.0	17-OHCS	3.5 mg/day	2.2–7.3
GH	1.7 ng/ml	0.17–1.41	17-KS	3.4 mg/day	2.4–11.0
IGF-I	25 ng/ml	121–436	Estradiol	6 μg/day	<2.1
PRL	11.3 ng/ml	1.0–13.9			

17α-OHP: 17α-hydroxy progesterone, DHEA-S: dehydroepiandrosterone sulfate, 17-OHCS: 17-hydroxy corticosteroid, 17-KS: 17-ketosteroid

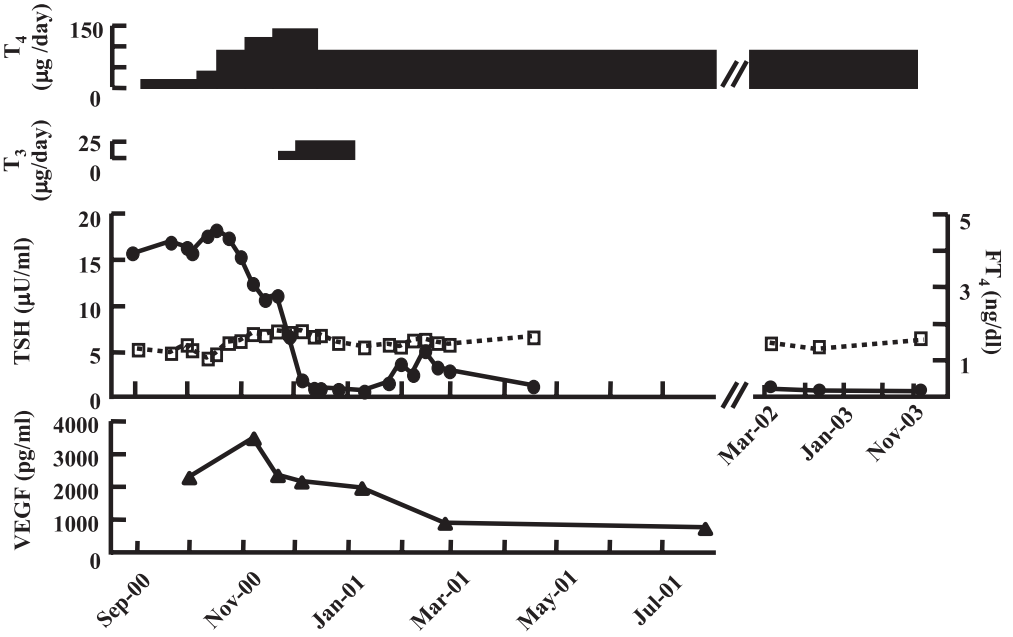

Fig. 3. Changes in TSH (●), FT_4 (□) and VEGF (▲) concentrations over time. Thyroid hormone treatment is indicated by the upper graph.

Table 3. Changes in TSH, gonadotropin, E2 and cytokines

	Oct 2000	Nov	Dec	Jan 2001	Feb	Jul	Reference interval
TSH (μU/ml)	15.4	12.0	0.25	0.04	2.7		0.41–4.0
LH (mIU/ml)	0.83		37.0	28.9		30.0	>4.2
FSH (mIU/ml)	10.6		49.0	47.0		78.0	>12.6
E2 (pg/ml)	55	42	19	<16		<16	<16
VEGF (pg/ml)	2289.9	3492.6		1974.0	896.6	754.8	62–707
IL-6 (pg/ml)	7.3			5.7		1.6	<4.0

creased to 150 μg/day. Because her TSH had not been normalized by 150 μg/day T_4, liothyroninesodium (T_3) was added at a dose of 8.3 μg/day in addition to T_4 from November and then gradually increased to 25 μg/day. In December, her TSH moved into normal range, and thereafter TSH and thyroid hormone levels were maintained within normal range at a dose of only 100 μg/day T_4 (Fig. 3).

Pleural effusions and peripheral edema were remarkably improved after the decrease of TSH (Fig. 1B, 2B). In addition, the abnormality of LH, FSH and E2 were ameliorated following the improvement of thyroid function (Table 3). Similarly, VEGF and IL-6 levels were decreased. Almost all symptoms and signs were improved after thyroid hormone replacement therapy. Her clinical condition has remained stable for several years.

Discussion

The biochemical state characterized by an elevated serum TSH level with a concomitant normal FT_4 level has received a variety of designations, including mild thyroid failure, as well as compensated, early, latent, mild, minimally symptomatic, and preclinical hypothyroidism [2]. The most widely applied designation for this biochemical state is subclinical hypothyroidism, despite the fact that the meaning is somewhat ambiguous [1–3]. Although it is commonly believed that subclinical hypothyroidism usually represents mild clinical signs, our patient had severe clinical manifestations such as marked pleural effusions and peripheral edema. Pleural effusions have been reported to be associated with the duration rather than the degree of biochemical hypothyroidism [6, 19]. Furthermore, tissue hypothyroidism at the peripheral target organs may be different in the individual patient. Zulewski *et al.* showed that some patients with severe biochemical hypothyroidism had only mild clinical signs, whereas other patients with minor biochemical changes had quite severe clinical hypothyroidism [20]. On the other hand, although her thyroid function showed slightly elevated TSH, she needed 100 μg/day T_4 to maintain TSH within normal range, which is the dosage usually used for moderate to severe hypothyroid patients. TSH measurement has a high diagnostic accuracy for the early detection of primary hypothyroidism. However, TSH may be a poor measure of the clinical and metabolic severity of hypothyroidism, because TSH is maximally stimulated in the early stages of primary thyroid failure, with no further increase occurring with greater severity of hypothyroidism [4]. In addition, TSH levels are reduced in prolonged critical illness, compared with the acute situation [21]. These findings suggest that a major change in thyroid hormone set point regulation may occur. Our observation indicates that even biochemical subclinical hypothyroidism causes severe clinical manifestations and the judgment of severity in subclinical hypothyroidism should be guided by clinical presentation and not only by serum TSH concentration.

The accumulation of fluid in serous body cavities in hypothyroidism is frequently recognized, the most common sites being the pleural, peritoneal and pericardial cavities. It was reported that pleural effusions secondary to hypothyroidism were small, noninflammatory effusions that have characteristics between transdates and exudates [6] and are frequently associated with marked ascites [19]. The precise mechanism by which these effusions develop is not well known. Parving *et al.* demonstrated the combination of increased extravasations of plasma proteins and lack of a compensatory increase in lymph flow and protein return rate [22], and suggested this as the cause of exudates in serous cavities. Lange demonstrated that the capillary permeability increased with leakage of plasma proteins in state of hypothyroidism and that the permeability rapidly returned to normal with thyroid hormone therapy [7]. Recently, elevation of VEGF has been reported in POEMS syndrome, which often accompanies extravascular volume overload [14]. VEGF induces a rapid and reversible increase in vascular permeability, and it is thought that these functions may cause the development of clinical manifestations, including ascites, pleural effusion, peripheral edema and organomegaly in this syndrome. An association of edema with increased VEGF levels has also been demonstrated in other pathological conditions, such as ovarian hyperstimulation syndrome [15], preeclampsia [16], and diabetic patients with troglitazone treatment [17]. In our case, VEGF was elevated in the initial course of the episode and was then reduced with improvement of pleural effusions and peripheral edema after thyroid hormone replacement therapy. Therefore, it seems that VEGF has, at least partly, contributed as a primary pathogenic factor of pleural effusions and peripheral edema in our case, as well as in POEMS syndrome.

VEGF is known to be expressed in a number of normal adult tissues, including the kidney, lung, uterus, ovary, brain, heart, skin, pituitary gland, and macrophages [23]. It has been demonstrated *in vitro* that VEGF is produced by thyroid follicular epithelial cells in response to stimulation of the TSH receptor [24–27]. Secreted VEGF stimulates VEGF receptors (Flt family) on endothelial cells of thiouracil-fed rats in a TSH-dependent paracrine mechanism, leading to proliferation of endothelial cells and hypervascularity of the thyroid gland [24, 26]. Recently, Klein *et al.* demonstrated that recombinant human TSH (rhTSH) stimulation for 3 weeks induced local VEGF expression in normal human thyroid, which were grafted into nude mice [28]. Moreover, Iitaka *et al.* showed that serum VEGF levels are positively correlated with TSH levels in patients with Hashimoto's thyroiditis [29]. However, conflicting results have been reported both *in vitro* and *in vivo* [30–33]. Sorvillo *et al.* demonstrated that a short-term administration of rhTSH in patients induces a significant reduction in serum VEGF levels [31], whereas, Tuttle *et al.* did not observe any difference in serum VEGF levels in patients after short-term stimulation rhTSH [32]. Therefore, the duration of TSH stimulation *in vivo* may be critical in determining the response of VEGF production. Furthermore, Sorvillo *et al.* showed that TSH *in vivo* might be able to regulate VEGF production from many extrathyroidal tissues [31]. A possible explanation of this case is that VEGF might be increased by prolonged stimulation of TSH, and that it might then be produced from tissues other than the thyroid gland because her thyroid gland was atrophic. Secreted VEGF might subsequently stimulate VEGF receptors on endothelial cells, leading to increase in vascular permeability, and develop pleural effusions and peripheral edema.

In our patient, estrogen levels were increased in spite of being postmenopausal and decreased after thyroid hormone replacement. Thyroid hormone has been demonstrated to affect the clearance rate of estrogen and the peripheral aromatization of androgen [34, 35]. Longcope *et al*. demonstrated that hypothyroidism results in a decrease in the metabolic clearance rates of androstenedione (A) and estrone (E1), and an increase in peripheral aromatization of A to E1 [35]. The peripheral aromatization of androgens is a major source of estrogens in men and postmenopausal women, and an increase in peripheral aromatization might have led to the elevation of serum estrogen levels in our patient. An estrogen-responsive element in the promoter region of the gene for VEGF has been identified [36], that interacts with both ER-α and ER-β. Indeed, serum VEGF levels are higher in premenopausal women compared with postmenopausal women [37]. Furthermore, estrogen replacement therapy increased serum VEGF levels in postmenopausal women [37–39]. Therefore, increased estrogen, caused by hypothyroidism, also might have partially contributed to the elevation of serum VEGF levels in our patient.

In summary, we present a case of subclinical hypothyroidism with severe clinical manifestations. After thyroid hormone replacement therapy, elevated VEGF levels were decreased with improvement of pleural effusions and peripheral edema. Our observations indicate that even biochemical subclinical hypothyroidism causes severe clinical manifestations. Furthermore, these observations lead us to speculate that elevated VEGF may be a potential factor in the course of pathogenesis of pleural effusions and peripheral edema in hypothyroid patients.

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