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# Pitting type of pretibial edema in a patient with silent thyroiditis successfully treated by angiotensin ii receptor blockade

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Patient:** Female, 56
**Final Diagnosis:** Thyroiditis – silent
**Symptoms:** Palpitations • pretibial pitting edema • short of breath • sweating
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Endocrinology and Metabolic

**Objective:** Unknown etiology

**Background:** Hyper- or hypothyroidism sometimes causes pretibial myxedema characterized by non-pitting infiltration of a proteinaceous ground substance. However, in those patients, the "pitting" type of pretibial edema as a result of increased sodium and fluid retention or vascular hyper-permeability rarely occurs, except in cases complicated by heart failures due to severe cardiomyopathy or pulmonary hypertension.

**Case Report:** A 56-year-old woman developed bilateral pretibial pitting edema, followed by occasional sweating, palpitations, and shortness of breath, which persisted for more than 2 months. The diagnosis of hyperthyroidism due to silent thyroiditis was supported by elevated levels of free thyroxine (T4) and triiodothyronine (T3), with a marked decrease in thyroid-stimulating hormone (TSH), and the negative results for TSH receptor antibodies with typical findings of destructive thyrotoxicosis. Despite her "pitting" type of pretibial edema, a chest radiograph demonstrated the absence of cardiomyopathy or congestive heart failure. Oral administration of angiotensin II receptor blocker (ARB) was initiated for her systolic hypertension, with a relatively higher elevation of plasma renin activity compared to that of the aldosterone level. Although the symptoms characteristic to hyperthyroidism, such as increased sweating, palpitations and shortness of breath, slowly improved with a spontaneous resolution of the disease, ARB quickly resolved the pretibial pitting edema shortly after the administration..

**Conclusions:** In this case, increased activity of the renin-angiotensin-aldosterone system stimulated by thyroid hormone was likely responsible for the patient's pitting type of edema. The pharmacological blockade of the renin-angiotensin-aldosterone system was thought to be effective for the quick resolution of the symptom.

**MeSH Keywords:** Renin-Angiotensin System • Hyperthyroidism • Thyroiditis

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## Background

Hyperthyroidism is a condition that results from the effects of excessive amounts of thyroid hormones on body tissues [1]. The classic symptoms of hyperthyroidism include a fine tremor, palpitations, heat intolerance, weight loss, anxiety, increased bowel movements, and shortness of breath. In patients with other endocrine disorders, such as Cushing's syndrome and hypothyroidism, systemic edema occurs most prominently in the pretibial region [2,3]. Although this symptom is quite common in such patients, it is not the case in patients with hyperthyroidism. Nevertheless, among diseases that cause hyperthyroidism, such as Graves' disease, toxic adenoma, and subacute or silent thyroiditis [4–6], Graves' disease alone sometimes causes pretibial myxedema characterized by non-pitting infiltration of a proteinaceous ground substance [7]. Recently, Volke et al. reported a case of Graves's disease complicated by pretibial pitting edema, although the pathophysiological mechanism was unknown [8]. However, in patients with hyperthyroidism, the "pitting" type of pretibial edema as a result of increased sodium and fluid retention or vascular hyper-permeability rarely occurs, except in cases complicated by heart failures due to severe cardiomyopathy or pulmonary hypertension [9,10].

## Case Report

A 56-year-old woman with no apparent past medical history came to our outpatient clinic because of bilateral pretibial pitting edema that developed 2 months prior to her visit. Over the past 6 months, she had occasionally noticed increased sweating, palpitations, and shortness of breath. On physical examination, the patient appeared exhausted. Her body temperature was 36.5°C, blood pressure was 152/83 mmHg, and pulse rate was 88 beats/min. She weighed 75 kg and was 160 cm tall. Her skin was moist and slightly warm. Although she had no swelling in her face, both her legs had pitting edema in the pretibial, but not in the ankle, region. There was no pain or redness in the pretibial region and calves. On examination of the head and neck, there were no signs of ophthalmopathy and her thyroid gland was not palpable. The jugular veins were not dilated. No murmurs or a 3$^{rd}$ sound were heard on cardiac auscultation, and no crackles or wheezes were heard on lung auscultation. The liver and spleen were not palpable. Laboratory data showed a normal peripheral white blood cell count (4800/µl) without anemia (hemoglobin 13.4 g/dl, hematocrit 40.1%) or severe hypoproteinemia (serum protein 7.1 g/dl, albumin 3.7 g/dl). Other routine laboratory test results, including blood glucose level, erythrocyte sedimentation rate, electrolytes, and kidney and liver function test results (e.g., serum creatinine and liver enzyme levels) were normal. The coagulation parameters, such as D-dimer, were not significantly elevated (0.88 µg/ml). The urinalysis revealed negative results for both proteinuria and hematuria. Although endocrine studies demonstrated normal levels of serum cortisol and catecholamines, the levels of free thyroxine (T4) and triiodothyronine (T3) were both elevated (free T4 4.7 ng/dl, normal 0.8–1.8; free T3 12.7 pg/ml, normal 2.3–4.2), and the level of thyroid-stimulating hormone (TSH) was markedly suppressed (0.013 µIU/ml, normal 0.5–4.7). These laboratory findings and the clinical symptoms, such as increased sweating, palpitations and shortness of breath, indicated the presence of hyperthyroidism. Both the plasma renin activity (PRA) and aldosterone level were within normal ranges (PRA 2.3 ng/ml/hr, aldosterone 68 pg/ml). However, as previously demonstrated in patients with hyperthyroidism [11,12], a relatively higher elevation of PRA compared to that of aldosterone level strongly suggested increased activity of the renin-angiotensin-aldosterone system. Electrocardiogram did not show any paroxysmal arrhythmias, such as atrial fibrillation, and a chest radiograph showed a normal cardiothoracic ratio, demonstrating the absence of cardiac enlargement. Echocardiography did not show the increase in pulmonary artery pressure and cardiac output, indicating the absence of pulmonary hypertension or cardiomyopathy.

Serum antibodies against TSH receptor (TSHR-Ab, which was based on the human monoclonal autoantibody M22) [13], thyroglobulin, and thyroid peroxidase (TPO) (polyclonal) were all negative. According to the literature [14], the absence of TSHR-Ab in serum does not always exclude the possibility of Graves' hyperthyroidism. However, in the present case, since ultrasonographic findings of the neck demonstrated a slightly hypoechogenic, but normal-sized, thyroid gland without nodular structures and hyper-vascularization, Graves' disease was not likely to be the diagnosis. Although a radioiodine uptake scan was thought to be useful for the differential diagnosis, we did not perform the examination. Instead, the ultrasonographic findings were considered to be enough to support a diagnosis of silent thyroiditis. Additionally, in our case, the calculated ratio of free T4 to free T3 was 2.70, which was lower than its cutoff point [15]. This may indicate the possibility of destructive thyrotoxicosis rather than Graves' disease, for which no causal treatment was required. However, since the patient presented systolic hypertension, and since the renin-angiotensin-aldosterone system was thought to be activated, oral administration of an angiotensin II receptor blocker, valsartan (40 mg/day), was immediately started after the diagnosis (Figure 1). Within a few days after the initiation of the drug, the patient's pretibial pitting edema quickly disappeared without any recurrence afterwards (Figure 1), indicating complete remission of the symptom. In contrast, however, other symptoms that are characteristic of hyperthyroidism, such as increased sweating, palpitations, and shortness of breath, slowly improved with the spontaneous resolution of

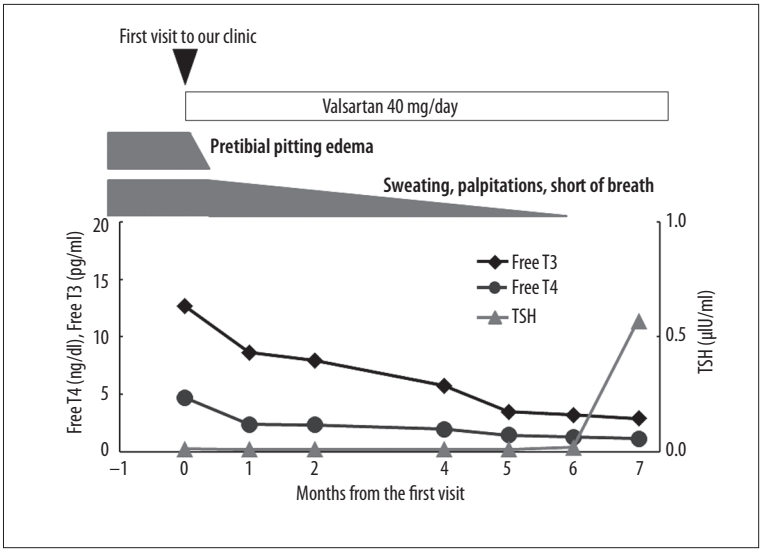


**Figure 1.** Clinical course and the changes in free thyroxine (T4), free triiodothyronine (T3), and thyroid-stimulating hormone (TSH). Symptoms such as increased sweating, palpitations, and shortness of breath slowly improved with the spontaneous resolution of hyperthyroidism. However, valsartan quickly resolved pretibial pitting edema shortly after the administration, and there were no further signs of recurrence with the continuous administration of the drug. T4 – thyroxine; T3 – triiodothyronine; TSH – thyroid-stimulating hormone.

the disease (Figure 1). By 5 months after her first visit, the patient became euthyroid (free T4 1.44 ng/dl, free T3 3.47 pg/ml). After 7-month follow-up, her TSH level returned to within the normal range (0.57 μIU/ml) (Figure 1), which was not followed by a hypothyroidic phase thereafter, although it is often the case with silent thyroiditis.

## Discussion

Cardiac output is often increased in patients with hyperthyroidism due to the increase in peripheral oxygen demand and the cardiac contractility [16]. In such patients, therefore, long-term exposure to thyroxine sometimes causes the development of cardiomyopathy [17]. Occasionally, congestive heart failure as a result of severe cardiomyopathy can cause the "pitting" type of pretibial edema as a local sign of systemic edema [9]. Recently, pulmonary hypertension has also been recognized as a complication of hyperthyroidism [18]. It can also cause the "pitting" type of pretibial edema as a result of right-sided heart failure [10]. Otherwise, such clinical manifestations are extremely rare in patients with hyperthyroidism. In our case, although the patient presented pretibial pitting edema, cardiomyopathy or pulmonary hypertension were not likely the causes of her symptom, since the heart was not enlarged and pulmonary artery pressure was not increased in the echocardiography. Additionally, the laboratory findings indicated the absence of other causes of systemic edema, such as nephrotic syndrome, liver disease, severe hypoalbuminemia, and Cushing's syndrome. The absence of pain or redness in the calves, in addition to a negative result for D-dimer, also indicated a low likelihood of deep vein thrombosis. Since the patient's plasma renin activity was relatively elevated, and since the pharmacological blockade of angiotensin II receptor quickly resolved the pretibial pitting edema in contrast to the slow improvement of other hyperthyroidic symptoms (Figure 1), the activation of the renin-angiotensin-aldosterone system was thought to be responsible for her edema.

Since thyroid hormone activates the adrenergic nervous system [19], most symptoms caused by hyperthyroidism are commonly treated by beta-adrenergic blockers, such as propranolol [20]. According to several *in vivo* studies, however, this hormone stimulates renal renin synthesis without affecting the adrenergic nervous activity [21,22]. Previously, Peti-Peterdi et al. demonstrated in *in vitro* studies that the increased expression of cyclooxygenase-2 (COX-2) and the production of prostaglandin $E_2$ ($PGE_2$) in macula densa cells stimulate renal renin synthesis from juxtaglomerular cells [23–25]. Recently, we have further demonstrated in animal studies that the increase in renal $PGE_2$ was actually associated with the increase in local renin production [26]. Since thyroid hormone is known to positively regulate the renal expression of COX-2 and $PGE_2$ [27], this hormone was thought to stimulate renal renin synthesis by increasing the local production of COX-2 and $PGE_2$ in the kidney. In our case, the activity of the renin-angiotensin-aldosterone system was thought to be elevated, and its pharmacological blockade by valsartan effectively resolved the edema. Additionally, based on the mechanism described above, the use of COX inhibitors, such as nonsteroidal anti-inflammatory drugs (NSAIDs) [28], or the use of selective COX-2 inhibitors [29], may also be beneficial for the quick resolution of pitting edema in patients with hyperthyroidism.

## Conclusions

This is the first report of a patient with hyperthyroidism due to silent thyroiditis, who presented pretibial pitting edema in the absence of cardiomyopathy or pulmonary hypertension.

In this case, increased activity of the renin-angiotensin-aldosterone system stimulated by thyroid hormone was likely responsible for the symptom. In this case, the pitting edema was successfully treated by the pharmacological blockade of the renin-angiotensin-aldosterone system.

**Declaration of interest**

The authors declare no conflicts of interest.

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