Increased Thyroid Blood Flow in the Hypoechoic Lesions in Patients with Recurrent, Painful Hashimoto’s Thyroiditis at the Time of Acute Exacerbation

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Abstract. We report two cases with painful Hashimoto’s thyroiditis, who developed recurrent fever and painful thyroid. Glucocorticoid treatment was transiently successful but tenderness in the thyroid gland and fever developed when glucocorticoid was tapered. One patient underwent total thyroidectomy uneventfully. As is well known, it is frequently difficult to make differential diagnosis between painful Hashimoto’s thyroiditis and subacute thyroiditis particularly at the initial phase. Interestingly, color flow doppler sonography of patient 1 revealed an increased thyroid blood flow in the hypoechoic lesions at the time of acute exacerbation although the serum level of TSH was suppressed. In the other patient, thyroid blood flow was also increased mainly in the hypoechoic lesions when the serum level of TSH was moderately increased, and it disappeared completely after supplementation of prednisolone and L-T4. Since thyroid blood flow in subacute thyroiditis is always decreased, such an increased blood flow in the hypoechoic lesion may be one of clinical characteristics of painful Hashimoto’s thyroiditis, and useful for differential diagnosis from subacute thyroiditis.

Key words: Chronic Thyroiditis, Color flow Doppler sonography, Thyroid blood flow

PATIENTS with chronic lymphocytic thyroiditis, or Hashimoto’s thyroiditis (HT), usually present with non-tender diffuse goiter and hypothyroidism. However, in a very few cases, they complained of thyroid pain and tenderness, accompanied with fever and general malaise [1]. Since C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) frequently slightly or moderately (but not extremely) increased, these painful Hashimoto’s thyroiditis is frequently diagnosed as subacute thyroiditis [1–6]. In contrast to subacute thyroiditis, painful Hashimoto’s thyroiditis is only temporary responsive to glucocorticoid treatment, and frequently relapses when glucocorticoid is tapered or discontinued. Therefore, total thyroidectomy is recommended for recurrent, painful Hashimoto’s thyroiditis when the disease is relapsing for a prolonged period [1–6].

Blood flow in the thyroid gland is usually regulated by TSH receptor stimulation [7, 8]. When TSH receptor is stimulated, vascular endothelial growth factors, mainly VEGF-A, VEGF-B, and placental growth factor (PIGF) mRNA increase [9, 10]. These angiogenesis factors synergistically stimulate VEGF receptors expressed on endothelial cells [7, 11, 12], leading to hypervascularity of thyroid gland. Therefore, thyroid blood flow is markedly increased in thyroid-stimulat-
ing antibody (TSAb)-positive patients with Graves’ disease. Furthermore it is also increased in some patients with chronic thyroiditis in whom serum TSH is markedly elevated [13]. This is also the case in iodine-induced primary hypothyroidism when excessive intake of iodine was discontinued [14].

Although thyroid blood flow is decreased in patients with inflammatory thyroid disease such as subacute thyroiditis [15, 16], we report two cases with painful Hashimoto’s thyroiditis in whom color flow Doppler sonography (CFDS) revealed an increased thyroid blood flow chiefly in the hypoechoic lesions at the time of acute exacerbation, even though TSH was suppressed.

Case report

Patient 1

A 58-years-old woman visited the Institute of Clinical Endocrinology, Tokyo Women’s Medical University because of recurrent painful thyroiditis in the mid of July, 2004. Six years ago, the patient had been diagnosed with Hashimoto’s thyroiditis at a nearby hospital. The thyroid was diffusely enlarged and anti-thyroglobulin antibody was strongly positive (1:1,638,400; reference range <100) (Table 1A). The patient was prescribed with L-thyroxine at a daily dose of 75 μg and had been euthyroid. At the end of June 2004, the patient developed fever accompanied with tenderness in the right thyroid lobe. Serum level of TSH was suppressed to 0.017 μU/ml, with normal serum levels of fT3 and fT4. CRP was positive (4.39 mg/dl). On a diagnosis of subacute thyroiditis, the patient received prednisolone at a daily dose of 20 mg. Thyroid pain and fever subsided and glucocorticoid was tapered off at the beginning of July. One week later, she developed fever (38°C), and the right lobe became painful and visited our out-patient clinic taking prednisolone 10 mg and L-thyroxine 50 μg daily.

The patient was 155 cm tall and the body weight (58 kg) was unchanged. The thyroid gland was diffusely enlarged and very hard. The patient complained of tenderness in the right lobe that was recently enlarged. CBC was normal (WBC 8,080/mm³, Hb 13.6 g/dl, RBC 448 × 10⁶/mm³, Ht 42.4%). CRP (0.06 mg/dl) was normal (<0.33). ESR was 20 mm/h. Serum level of TSH was suppressed to 0.07 μU/ml (reference range; 0.38–4.3 μU/ml). Serum levels of T3 and T4 were 0.73 ng/ml (0.76–1.5 ng/ml) and 7.3 μg/dl (5.7–11.1 μg/dl), respectively. Because of a markedly increased anti-thyroglobulin antibody (3,900 U/ml; reference range <0.3 U/ml), thyroglobulin was undetectable. Ultrasonography revealed a diffusely enlarged thyroid gland (the right lobe 74 × 21 × 19 mm, the left lobe 37 × 15 × 13 mm, isthmus 4.5 mm). The internal echo was inhomogenous. There was large low echoic lesions in the right lobe and left lobe (Fig. 1A), and CFDS revealed an increased thyroid blood flow in the hypoechoic lesion (Fig. 1B).

On a tentative diagnosis of subacute thyroiditis or acute exacerbation of chronic thyroiditis, prednisolone was prescribed immediately at a daily dose of 30 mg. Fever and tenderness in the thyroid gland resolved gradually. Prednisolone was slowly tapered. The thyroid gland volume was not changed in August (the right lobe; 66 × 23 × 20 mm, the left lobe; 46 × 14 × 11 mm), however, the low echoic lesion was increased in the both lobes and CFDS revealed also an increased blood flow in the low echoic lesions (Fig. 1C). A daily dose of prednisolone was decreased to 10 mg in November. The patient had no tenderness in the thyroid gland, and the increased thyroid blood flow in the low echoic lesions was markedly decreased. When prednisolone dose was reduced to 7.5 mg daily in the mid of December, thyroid pain and swelling recurred. Serum levels of TSH, T3, and T4 were 0.30 μU/ml, 0.85 ng/ml, and 7.1 μg/dl, respectively. The thyroid gland was diffusely enlarged (the right lobe 67 × 25 × 23 mm, the left lobe 34 × 17 × 13 mm) with low echoic lesions in the both lobes. CFDS also revealed an increased blood flow in the low echoic lesion (Fig. 1D). Biopsy performed at the same time revealed that the thyroid follicles were normal in the superficial region of the thyroid with a local infiltration of a number of small lymphocytes but were atrophic with diffuse infiltration of small lymphocytes associated with fibrosis in the deep lesion (Fig. 1E & F). No giant cell was observed, and the diagnosis of chronic thyroiditis was confirmed.

The dose of prednisolone was increased to 30 mg again, and the symptoms resolved. However, when prednisolone was gradually tapered to 5–7.5 mg/day, fever and pain in the thyroid gland developed again. Although we recommended total thyroidectomy, the patient did not agree, and she was lost to follow-up.
Patient 2

A 50-years-old woman developed general malaise and visited a nearby hospital in March 2003. A very hard nodular lesion was felt in the both thyroid lobe. Serum level of TSH was suppressed to <0.05 μU/ml, accompanied with elevated serum levels of fT4 (5.14 ng/dl) and fT3 (9.5 pg/ml) (Table 1B). TRAb was slightly positive (18.6%). Although painless thyroiditis could not be ruled out, the patient was diagnosed to have developed Graves’ disease, and treated with methimazole. Thyroid function became rapidly hypothyroid in three months, and methimazole was discontinued, and L-thyroxine (50 μg) was prescribed. However, fever and tenderness in the thyroid gland recurred in December. At the beginning of January 2004, the serum levels of TSH, fT4, and fT3 were 0.12 μU/ml, 1.81 ng/dl, and 3.0 pg/ml, respectively. CRP was strongly positive. Thyroidal [123]I uptake was 4.7% at 4h and 9.5% at 24h. On a tentative diagnosis of subacute thyroiditis, prednisolone was administered at a daily dose of 30 mg. Fever and pains in the thyroid gland resolved. However, when the dose was reduced to 10 mg daily, fever and tenderness in the thyroid gland recurred again. The patient had mild diabetes mellitus that exacerbated to require insulin therapy in April 2004. The patient was prescribed with prednisolone 10 and 15 mg on alternate days, and referred to our hospital in July 2004.

The patient was 154 cm tall, and the body weight (53.8 kg) was unchanged. The thyroid gland was diffusely hard, but non-tender on palpation. Serum level
of TSH was increased to 44.2 μU/ml, with decreased serum levels of fT4 (0.51 ng/dl) and fT3 (0.93 pg/ml). TRAb was negative (~2.5%). CRP was normal (0.19 mg/dl). Thyroglobulin antibody was so strongly positive (22,800 U/ml, reference range <0.3 U/ml) that thyroglobulin could not be detected (<5 ng/ml). Ultrasoundography revealed a non-enlarged thyroid gland (the right lobe: 38 × 20 × 25 mm, the left lobe: 43 × 15 × 23 mm). Internal echo was inhomogenous, and low echoic lesion with a diameter of 3 cm was observed in the both lobes (Fig. 2A). CFDS revealed an increased blood flow in the low echoic lesions in the both lobes.
Prednisolone was tapered to 10 mg/day and L-thyroxine (50 μg/day) was prescribed. In August, biopsy was performed. The thyroid follicles were atrophic with marked infiltration of lymphocytes. Advanced fibrosis was observed in the deep lesion (Fig. 2C, D, E). In October, serum levels of TSH and fT4 were 5.52 μU/ml and 1.24 ng/dl, respectively, Ultra-sonography revealed inhomogenous internal echo in the both thyroid lobes with low density lesion (37 × 24 mm in the right lobe, and 28 × 18 mm in the left lobe), and CFDS could not detect the increased blood flow in the low echoic lesion (Fig. 2F), suggesting that hypervascular inflammatory lesion has been replaced with hypovascular fibrous tissue.

(Fig. 2B)
The patient remained euthyroid with L-thyroxine (50 μg/day). Although treatment with corticosteroids was partially successful, iatrogenic Cushing’s syndrome such as moon face became evident, and type II diabetes mellitus was not well controlled with insulin. Therefore the patient underwent total thyroidectomy in November 2004. Because thyroid gland was small and very hard, total thyroidectomy was preformed by a skilled and experienced thyroid surgeon in our Institute. Consistent with the latest CFDS findings, the thyroid gland was not hypervascular at the operation, and the hard thyroid gland (25 g, the right lobe; 45 × 17 × 15 mm, the left lobe; 52 × 22 × 16 mm) was totally removed. The surgery was successful without any complications and the patients remained asymptomatic and did not require any further anti-inflammatory therapy. The patient had been euthyroid with maintenance dose of L-thyroxine (75 μg/day) for the last 4 years. Insulin was gradually tapered off in October 2005, and the patient is doing well only with diet therapy.

Discussion

Recurrent, painful Hashimoto’s thyroiditis has been referred to as painful chronic thyroiditis, acute exacerbation of Hashimoto’s thyroiditis, or painful variant of Hashimoto’s thyroiditis [1–6]. Clinical courses of the present cases, such as fever and recurrent thyroid pains, refractoriness to glucocorticoid treatment, normal or elevated CRP and/or ESR, non-suppressed thyroidal 123I uptake, were very similar to those reported previously [1–6]. The pathologic characteristics of thyroid tissue sections from these patients were basically not different from patients with non-tender Hashimoto’s thyroiditis. A variable degree of fibrosis with focal and diffuse infiltration of small lymphocytes was found on assessment of pathology specimens. Although painful Hashimoto’s thyroiditis is refractory to glucocorticoid therapy, these patients may frequently recede and become convalescent from it completely when repeatedly treated with glucocorticoids. However, in a few patients, painful thyroiditis may recur frequently when glucocorticoids are tapered. Therefore, total thyroidectomy is occasionally an effective and successful treatment in such cases as recommended by Kon and DeGroot [1].

Usually, blood flow in the thyroid gland is regulated by TSH receptor stimulation [7, 8]. When TSH receptor on thyroid follicles is stimulated, vascular endothelial growth factors, mainly VEGF-A, VEGF-B, and placental growth factor (PIGF) mRNA increase [9, 10]. These angiogenesis factors synergistically stimulate VEGF receptors expressed on endothelial cells [11, 12]. Since these endothelial cells fuse together, the diameter of capillary blood vessels increase [17], leading to increased blood flow in the thyroid gland. Therefore, thyroid blood flow is markedly increased in hyperthyroid patients with Graves’ disease. Increased blood flow is also observed in the parenchyma in some patients with hypothyroidism in whom serum TSH is markedly elevated [13, 14], whereas thyroid blood flow is decreased in acute thyrotoxic phase of subacute thyroiditis due to suppression of TSH [15, 16].

However, we found the increased thyroid blood flow in the hypoechoic lesions in 2 patients with recurrent, painful Hashimoto’s thyroiditis at the time of acute exacerbation (Fig. 1, 2). Since serum level of TSH was decreased in patient 1, the increased blood flow was not due to TSH receptor stimulation. Furthermore, although serum level of TSH was moderately increased in patient 2, an increased blood flow was observed not in the parenchyma but only in hypoechoic lesions. These clinical observations suggest that increased blood flow is not due to overexpression of VEGF-A, VEGF-B, or PIGF in thyroid follicles.

In acute exacerbation of chronic thyroiditis, such as painful Hashimoto’s thyroiditis, a number of immunocompetent and inflammatory cells would be infiltrated into hypoechoic lesion, and produce various inflammatory cytokines, such as IL-1, TNF-α, IL-6, IL-8, and interferons [18]. Since these pyrogenic cytokines would be excessively produced in acute exacerbation of Hashimoto’s thyroiditis, they will be detected by the circumventricular organ system in the hypothalamus, leading to development of fever [18, 19]. Among VEGF family, VEGF-C mRNA expression is stimulated by IL-1 [20] and VEGF-C and its receptor (VEGFR3) is expressed in autoimmune thyroid diseases [21], suggesting that VEGF-C is at least in part involved in the hypervasularity in the hypochoic lesion in our present patients. Furthermore, a number of macrophages infiltrate into the inflammatory lesion and these activated macrophages produce various angiogenic factors (bFGF, TGF-α, VEGF, IL-8), leading to inflammatory angiogenesis [22]. In addition, prostaglandin endoperoxide synthase 2 (PGES2) or cy-
clooxygenase 2 (COX2) is usually induced in inflammatory tissues, and its expression is increased also in Hashimoto’s thyroiditis [23, 24]. Since these factors stimulate formation of inflammatory prostaglandins and NO [25], they are also involved in hypervascularity in the hypoechoic lesion in the present cases. Lastly, we would like to point out that our CFDS was preformed when the patients had been taking prednisolone at daily dose of 10 mg. Generally, glucocorticoids are supposed to suppress thyroid blood flow by decreasing production of inflammatory cytokines. Whether the increased thyroid blood flow is more markedly elevated before glucocorticoids are prescribed to patients with painful, recurrent Hashimoto’s thyroiditis at the time of acute exacerbation remains to be elucidated in the future studies.

Very recently, we reported that when human thyroid follicles were cultured with double-stranded RNA, type I IFN system was acutely activated, leading to remarkable production on IFN-β, an antiangiogenesis factor [22]. Since this in vitro experimental system can be regarded as a model of subacute thyroiditis [26], IFNs produced by viral infection may at least in part account for non-increased blood flow in the hypoechoic lesion in subacute thyroiditis.

Usually, the differential diagnosis between painful Hashimoto’s thyroiditis and subacute thyroiditis is difficult particularly at the initial phase. Laboratory features helpful in distinguishing painful Hashimoto’s thyroiditis from subacute (de Quervain’s) thyroiditis are normal or slightly increased erythrocyte sedimentation rate, non-suppressed 123I uptake, and a markedly increased antithyroid antibody titer [1–6]. Since an increased blood flow is not observed in acute phase of subacute thyroiditis [15, 16], we speculate that such an increased blood flow in the hypoechoic lesion is one of the clinical characteristics of painful Hashimoto’s thyroiditis. Indeed, a hyperemic hard thyroid was also observed in one of 7 patients who underwent subtotal thyroidectomy [1]. Although the pathophysiological mechanism by which an increased blood flow occurs in the hypoechoic lesions of painful Hashimoto’s thyroiditis at acute exacerbation remains to be elucidated, CFDS finding may be useful for differential diagnosis of painful Hashimoto’s thyroiditis and subacute thyroiditis.

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References


