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NOTE

Amyloid Goiter Presented as a Subacute Thyroiditis-Like Symptom in a Patient with Hypersensitivity Vasculitis

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Abstract. We present a 25-year-old woman with amyloid goiter due to hypersensitivity vasculitis, who developed transient thyrotoxicosis resembling subacute thyroiditis. She received prednisolone (20 mg/day) for three years for hypersensitivity vasculitis, and was diagnosed as having secondary amyloidosis by biopsies of the stomach, rectum and kidneys. She noticed neck swelling with severe right neck tenderness, palpitation, hyperhidrosis and weight loss. An elastic firm diffuse goiter was palpable, and the upper pole of the right lobe was extremely tender. Her serum free T4 and T3 levels were high, and the serum TSH was suppressed to subnormal. She was positive for serum C-reactive protein. Antithyroidal autoantibodies were all negative. Her thyrotoxicosis subsided spontaneously within one week. Serum titers of antibodies to various viruses were unchanged during the clinical course for two weeks, but she was positive for HLA B35. Examination of a needle-biopsy specimen of the thyroid gland showed extensive amyloid deposition and no evidence of subacute thyroiditis. We considered her transient thyrotoxicosis to be associated with amyloid goiter. The clinical course of this case was similar to the subacute thyroiditis-like syndrome, first described by Ikenoue et al. When patients with primary or secondary amyloidosis have symptoms and signs of subacute thyroiditis, but develop an unusual course, amyloid goiter should be considered.

Key words: Subacute thyroiditis-like syndrome, Amyloid goiter

AMYLOID goiter is characterized as an enlarged thyroid gland due to amyloid deposition in patients with primary or secondary amyloidosis [1-4]. In most cases, thyroid function is normal [3-5], but both hypo- and hyperthyroidism are also observed in patients with amyloid goiter [2, 4, 6, 7]. And five cases with amyloidosis were reported to have symptoms resembling subacute thyroiditis [8-11]. In 1988, Ikenoue et al. [11] first employed the term subacute thyroiditis-like syndrome (STLS) to describe the clinical state resembling subacute thyroiditis. Because of the limited number of cases, the clinical entity and pathogenesis of STLS remain unclear. We present a patient with secondary amyloidosis due to hypersensitivity vasculitis, who had amyloid goiter accompanied by transient thyrotoxicosis, resembling STLS.

Materials and Methods

 Serum levels of free thyroxine (FT4), free triiodothyronine (FT3), and thyroglobulin (Tg) were measured by radioimmunoassay (FT4 and FT3, Amersham International Ltd., Amersham, Bucks, UK; Tg, Eikenkagaku, Tokyo, Japan). TSH in serum was measured by a two-site immunoenzymometric assay (Tosoh, Yamaguchi, Japan). Anti-thyroglobulin (TgAb) and anti-thyroid peroxidase
antibodies (TPOAb) were assayed by RIA (RSR Ltd., Cardiff, UK). TSH binding inhibitor immunoglobulin (TBII) activity was measured by a radioreceptor assay (TRAb) with a commercially available kit (RSR Ltd., Cardiff, UK). Normal values were as follows: FT₄, 0.8–2.3 ng/dl; FT₃, 2.5–6.0 pg/ml; TSH, 0.3–4.5 µU/ml; Tg, <30 ng/ml; TgAb and TPOAb, <0.3 U/ml; TRAb, <15%.

Case Report

A 25-year-old woman was treated at our hospital for acute fatty liver complicated with hypersensitivity vasculitis in October, 1993 [12], and then given prednisolone (20 mg/day) for hypersensitivity vasculitis. In January, 1996 she was admitted to our hospital for ileus, and biopsies of the stomach, rectum and kidney revealed amyloid deposition indicating secondary amyloidosis. There was no abnormal finding in the thyroid gland on ultrasonography. Prednisolone (20 mg/day) was maintained for the treatment of hypersensitivity vasculitis.

In late July, 1996, one month after discharge, she noticed neck swelling with severe right neck tenderness, palpitation, hyperhidrosis and weight loss. Physical examination revealed that she was undernourished with 1.55 m height and 36.8 kg body weight. Her body temperature was normal. Her blood pressure was 110/70 mmHg, and the pulse rate 100 beats/min. She had no lid retraction, or tremor of fingers. An elastic firm diffuse goiter was palpable, and the upper pole of the right lobe was extremely tender. The laboratory data revealed a white blood cell count of 21500/mm³, with 93% neutrophils. The serum Na was 139 mEq/L, the serum K 3.8 mEq/L, and the C-reactive protein (CRP) 3.5 mg/dl. The serum cholesterol was 205 mg/dl. Her thyroid function was as follows: the serum FT₄ was 5.17 ng/dl, the FT₃ was 11.4 pg/ml, and the TSH was undetectable. The serum Tg concentration had increased to more than 1,000 ng/ml. Ultrasonography of the thyroid gland showed a slightly enlarged goiter (estimated thyroid volume 20.1 cm³) with irregular hypoechoic lesions in both lobes. Administration of a beta-adrenergic antagonist was initiated on July 31. Her serum FT₄ and FT₃ decreased to normal levels (1.79 ng/dl and 4.15 pg/ml, respectively) after one week, and thereafter the condition remained latent thyrotoxicosis. On August 15, her serum TSH level returned to normal (1.92 µU/ml) (Fig. 1). The serum Tg concentration decreased, but remained at a level above the normal range. Thereafter, her thyroid function has remained in a euthyroid state, except for a transient TSH increase from December, 1996 to March, 1997. Tg, thyroglobulin.

Fig. 1. Changes in thyroid function, white blood cell count (WBC), and serum C-reactive protein (CRP) levels. In late July, 1996, the serum FT₄, FT₃, and thyroglobulin were high, and the TSH was undetectable. Her thyrotoxicosis subsided spontaneously within one week. The serum thyroglobulin concentration decreased, but remained at a level above the normal range. Thereafter, her thyroid function has remained in a euthyroid state, except for a transient TSH increase from December, 1996 to March, 1997. Tg, thyroglobulin.
radioactive iodine uptake examined on August 27 was 12.2% (24 h) with a normal TSH level (2.19 μU/ml). Serum titers of antibodies to influenza, parainfluenza, mumps, measles, adenovirus, Epstein-Barr virus and coxsackievirus did not change. She was positive for HLA A24, A26, B35, B48, DR4, DR12, DQ3 and DQ4. The dose of prednisolone was unchanged throughout her clinical course.

A needle-biopsy specimen of the thyroid gland, obtained on September 6, showed extensive perifollicular deposition of amyloid, few follicular cells, and no evidence of subacute thyroiditis, leading to the histological diagnosis of amyloid goiter (Fig. 2). In addition, histological examination with antihuman amyloid A protein (AA) revealed diffuse deposition of AA protein in the thyroid gland. Since then, her serum FT4 and FT3 have remained normal for one year, but serum TSH transiently increased from December, 1996 to March, 1997.

Discussion

In our patient the findings inconsistent with subacute thyroiditis are: (1) there was no high fever, (2) thyroidal pain was not creeping, (3) thyrotoxicosis lasted for only two weeks, and (4) diffuse goiter persisted, even when she was in remission. We cannot deny the possibility that prednisolone would make her clinical course uncommon. On the other hand, our patient was positive for HLA B35, which is known to be associated with subacute thyroiditis [13, 14]. This haplotype seems to confer susceptibility to subacute thyroiditis, perhaps because it allows one or more viruses to trigger a cytotoxic T-cell response directed against thyrocytes. The needle-biopsy specimen showed marked amyloid deposition and few follicular cells, leading to the histological diagnosis of amyloid goiter. There are a various degrees of fibrosis and follicular degeneration in most patients with subacute thyroiditis, even if needle biopsy is performed one month after remission [15], but there was no evidence of subacute thyroiditis in our specimen. Moreover, the possibility of acute exacerbation of Hashimoto's thyroiditis, which is known to show the similar findings to those in our patient, is unlikely because anti-thyroidal autoantibodies were all negative and there was no evidence of Hashimoto's thyroiditis.

In our patient, the serum Tg concentrations remained above the normal range after a thyrotoxic state. The reason for this is not clear, but it is likely that Tg has been continuously released from newly damaged thyroid follicular cells. Another point to consider carefully is the fact that her serum FT4 and FT3 have remained normal in spite of the transient increase in serum TSH between December, 1996 and March, 1997. This clinical course of our patient is similar to that of about 60% of patients with painless thyroiditis, who show a mild inflammatory change in the thyroid gland [15]. The damaged thyroid follicular cells in our patient may therefore be localized and/or the severity of the destruction may be mild.

Amyloid deposition in the thyroid is found in about 30–80% of patients with primary or secondary amyloidosis [1]. In a few patients with amyloidosis, the thyroid is enlarged, and so-called amyloid goiter occurs. Thyroid function usually remains normal, but occasionally hypothyroidism or thyrotoxicosis occurs in patients with thyroid amyloidosis [2, 4, 6, 7]. When Ikenoue et al. [11] reviewed five patients with amyloid goiter and symptoms resembling subacute thyroiditis, they first used the term STLS to describe these symptoms. They described several characteristics of STLS in amyloid goiter. First, thyroidal pain is not creeping. Second, in contrast to other thyroid disorders [16], STLS in amyloid goiter seems to occur more frequently in
men than in women with a 4:1 ratio of male to female. But, because of the limited number of patients with STLS in amyloid goiter, the true ratio of male to female is unknown. Third, the associated diseases vary, that is, inflammatory bowel disease in two, tuberculosis in two, and rheumatoid arthritis in one. Our case was associated with hypersensitivity vasculitis. Fourth, there have been no reports of STLS in amyloid goiter from other countries. It is unclear whether Japanese are predisposed to STLS in amyloid goiter.

The pathogenesis of STLS in amyloid goiter remains unclear. Ikenoue et al. [11] did not mention the mechanism of the onset of STLS in thyroid amyloidosis. Tenderness of the thyroid gland may be caused by capsular stretching due to acute thyroidal enlargement [17], but the etiology of acute inflammation cannot be explained. Miaskiewicz et al. [18] reported amiodarone-induced thyrotoxicosis with an enlarged tender thyroid gland, similar to STLS in amyloid goiter. Amiodarone may induce destructive thyroiditis with the increase in serum interleukin 6 (IL-6) [19]. It is well known that IL-6 induces acute inflammatory changes, including increased CRP and accelerated erythrocyte sedimentation [20]. In addition, IL-6 has also been reported to be produced by thyrocytes [21, 22]. Histologically, amiodarone-induced destructive thyroiditis has destructive follicular lesions with intraluminal desquamation of cells, and zones of fibrosis containing small, distorted follicles [23], similar to STLS in amyloid goiter. If serum IL-6 levels increase in patients with STLS in amyloid goiter, acute inflammatory changes may occur. One possible trigger of the IL-6 release is the destruction of thyroid follicular cells due to ischemia or mechanical oppression by amyloid deposition, but the exact mechanism of the onset of STLS in amyloid goiter remains unknown, and further studies are needed.

References

AMYLOID GOITER AND TRANSIENT THYROTOXICOSIS