

## Two Cases-Report of Mild Graves' Disease Following Subacute Thyroiditis: More Evidence of the Role of Thyroglobulin in The Pathogenesis of Autoimmune Thyroid Disease?

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Rec date: April 16, 2015; Acc date: May 16, 2015; Pub date: April 24, 2015

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Keywords: Subacute thyroiditis; Grave's disease; Thyroglobulin; Anti- thyroglobulin antibodies

### Abstract

Two middle aged Caucasian women with no previous history of thyroid or any other disease developed typical subacute thyroiditis (SAT) with minimal thyroïdal radioactive iodine uptake. A few months after restoration of euthyroidism and discontinuation of corticosteroid therapy, they developed mild hyperthyroidism due to Graves' disease (GD), as judged by the increased diffuse thyroïdal radioactive iodine uptake. Both of them were genetically predisposed to the above diseases since they had the certain HLA haplotypes for SAT and GD. Also they developed anti- thyroglobulin antibodies during the period of GD. We hypothesize that genetic background and the increased load of Tg or other autoantigens released from the distracted damaged thyroid gland due to SAT triggered the development of GD a few months later.

### Introduction

Subacute thyroiditis (SAT) is an inflammatory disorder of the thyroid gland that is thought to be of viral origin [1]. It is considered a non-autoimmune disease, although a transient mild increase of titers of thyroid antibodies can be observed [2,3]. It seems to be especially common in genetically predisposed individuals who carry certain human leukocyte antigen (HLA) haplotypes [4].

Graves disease (GD) is an autoimmune thyroid disease and a model of organ specific autoimmunity. It is thought to be caused by a combination of genetic and environmental factors and initiated by the loss of immunological tolerance to thyroid restricted self antigens such as TSH receptor, thyroperoxidase and thyroglobulin [5]. The trigger for initiation of the immune response to the thyroid remains unknown in genetically predisposed individuals [6]. GD is strongly associated with certain HLA haplotypes, such as HLA-DRB1 and -DRB3 [6-8], as well as with polymorphisms in several other genes such as, in the Tg gene [9] and T-cell regulatory gene CTLA4 [10].

In our knowledge there are no reports for common HLA haplotypes related to subacute thyroiditis and Graves' disease.

The appearance of GD within a few months after SAT is rare, and only a few cases have been reported [11-17]. Also a case with simultaneous occurrence of subacute thyroiditis and Graves' disease has been described. However the authors suggest that SAT-induced autoimmunization may promote the development of Graves' disease in predisposed subjects and they do not support the hypothesis that there is a common mechanism for both diseases. Their patient was positive for both HLA-35 and HLA- DRB1antigens [18].

Here, we present two cases of SAT that developed GD 2-3 months after restoration of euthyroidism, and we discuss the possible

explanation for the transition of an inflammatory non-autoimmune to an autoimmune thyroid disease.

### Case 1

A 37-year-old Caucasian woman presented with fever, tenderness in the neck, and difficulty in swallowing for 15 days. Her medical history was free from disease. Physical examination revealed that the patient had an enlarged, diffuse, painful thyroid gland, a heart rate of 110 beats/min, a fine tremor, a warm skin, and a fast relaxation time of the Achilles tendon reflex. The patient's family history was negative for thyroid diseases. Laboratory examinations revealed: T3: 2.55 ng/ml (normal, 0.8-2.00 ng/ml); T4: 15.9 µg/dl (normal, 5.1-14.1 µg/dl); TSH: not detectable (nd); anti-TPO: 17 IU/ml (normal, <34 IU/ml); anti-Tg: 20 IU/ml (normal, <115 IU/ml); Tg: 403 ng/ml (normal, 1.4-78 ng/ml); erythrocyte sedimentation rate (ESR): 186 mmHg/h; and C-reactive protein (CRP): 9.3 mg/dl (normal, <0.80 mg/dl); white blood cell count was slightly higher than normal, whereas renal and liver function biochemical tests gave values within normal ranges. Ultrasonography showed an enlarged, heterogeneous, hypochoic thyroid gland without discrete nodules. Twenty-four hours after administration of a tracer dose of 5µCi <sup>131</sup>I, the thyroïdal radioactive iodine uptake (RAIU) was <1%. Following diagnosis of SAT, corticosteroids (prednisone 30 mg per day) and β-blockers (propranolol 30 mg per day) were administered. Pain subsided rapidly, and the symptoms had fully remitted within 3 weeks; then thyroid function tests (TFTs) were within the normal range and ESR was 3 mm in the first hour and the corticosteroid dose was gradually reduced and finally stopped 2 months later. One month later, SAT relapsed with the same clinical signs and symptoms. The values obtained from TFTs were: T3: 1.9 ng/ml; T4:14.3 µg/dl; TSH: not detectable (nd); and ESR: 86 mm in the first hour. A new 8-week course of corticosteroids

resulted in resolution of the symptoms and restoration of euthyroidism.

Three months later the patient returned to our outpatient clinic with fine tremor, sweating, tachycardia, irritability and denied ocular symptoms. Physical examination revealed a palpable non-painful thyroid gland. The values obtained from TFTs were TSH: nd; T3: 2.66 ng/ml; T4:12.5 µg/dl; Tg: 39 ng/ml; anti-TPO: 15 IU/ml; anti-Tg: 244 IU/ml; and ESR: 23 mm. Scintigraphy with 5 µCi <sup>131</sup>I revealed high uptake and a diffuse, enlarged thyroid gland, characteristic of hyperthyroidism and suggestive of GD. The patient was given 30 mg/day carbimazole and 30 mg/day propranolol for 2 months, and became slightly hypothyroid, with the following values obtained after TFTs: TSH: 7.99 µIU/ml; T3: 0.86 ng/ml; T4: 3.3 µg/dl; Tg: 39 ng/ml; anti-TPO: 24 IU/ml, anti-Tg: 522 IU/ml; and ESR: 23 mm. Thereafter, she remained euthyroid under low doses of carbimazole (5mg carbimazole/day) for 1 year. Since termination of carbimazole treatment, she has remained euthyroid without treatment for 2 years. HLA typing showed positivity for B35.03, DRB1 0301, and DRB1 1301.

## Case 2

A 55-year-old Caucasian woman presented with fever for 15 days, as well as neck pain, palpitations, sweating, and fatigue. Her medical history was free from disease. On physical examination she had an enlarged painful thyroid gland, heart rate of 120 beats/min, fine tremor, and rapid relaxation time of the Achilles tendon reflex. Laboratory examination showed: TSH: 0.01 µIU/ml; FT3: 9.2 pmol/l (normal, 3.1–6.8 pmol/l); FT4: 3.18 ng/dl (normal, 0.8–2.00 ng/dl); Tg: 450 ng/ml (normal, 1.4-78 ng/ml); anti-TPO: 15.1 IU/ml; anti-Tg: 83.1 IU/ml; CRP: 14 mg/dl; and ESR: 98 mm/h. Thyroid ultrasonography showed an enlarged, heterogeneous, hypoechoic thyroid gland without discrete nodules. Twenty-four hours after administration of a tracer dose of 5 µCi <sup>131</sup>I, the RAIU value was <1%. The patient was prescribed 3 g/day acetylsalicylic acid and 30 mg/day propranolol, without remission of symptoms. Five days later, acetylsalicylic acid was replaced by 32 mg/day methylprednisolone for 20 days and tapered for the next 2 months. At that time, ESR was 20 mm/h and the patient was euthyroid. One month after glucocorticoid discontinuation, the patient presented again with symptoms of hyperthyroidism, such as palpitations, irritability, sweating, mild neck pain but without fever. She had TSH: nd; T3: 3.1 ng/ml; FT4: 1.84 ng/dl; CRP: 0.5 mg/dl; ESR: 80 mm; anti-TPO: 10.9 IU/ml; and anti-Tg: 121.9 IU/ml. A new course of 32 mg/day methylprednisolone and 30 mg/day propranolol was administered for the next 3 months, after which she became euthyroid and had TSH: 1.7 µIU/ml; T3: 1.21 ng/ml; T4: 6.6 µg/dl; and ESR: 17 mm/h. One month later, she complained of palpitations, arthralgia but without either fever or neck pain, and denied ocular symptoms. Biochemical evaluation revealed overt hyperthyroidism: TSH: nd; T3: 3.13 ng/ml; FT4: 2.48 ng/dl; anti-TPO: 20 IU/ml; anti-Tg: 237.6 IU/ml ESR 30 mm/h. Scintigraphy with 5 µCi <sup>131</sup>I revealed high uptake and a diffuse enlarged thyroid gland as in GD. Methimazole was started at 30 mg/day, as well as 30 mg/day propranolol and gradually tapered and stopped as she became euthyroid 1 year later. She has remained euthyroid without therapy for 1 and a half year. HLA haplotyping revealed B35, 51 and DRB1\*11XX and 13XX.

## Discussion

We have described two rare cases where SAT was followed within a few months by GD in two Caucasian women. Only a few similar cases have been reported in the literature [11-17].

It is well known that SAT is a non-autoimmune disease, but it is a self-limited inflammatory disorder of viral origin in genetically predisposed individuals [4]. A strong association between SAT and HLA-B35 in certain ethnic groups has been found, as well as there being reports of development of SAT in the same family [19] and identical twins who were heterozygous for HLA-B35 [20,21]. The thyroid tissue damage of the viral infection provides an antigen that uniquely binds to HLA-B35 molecules on macrophages. The resultant antigen-HLA-B35 complex activates cytotoxic T lymphocytes that in turn injure the thyroid follicular cells because the latter share the same antigen. Both of our patients had the HLA-B35 haplotype.

In contrast, GD is a well-established autoimmune disorder. Thyroid epithelial cells from patients with GD express HLA class II molecules; notably HLA-DRB1 and HLA-DRB3[8]. Expression of HLA molecules on thyroid cells, in individuals with the appropriate repertoire of HLA antigens, could be the result of viral infections, or it may be induced by cytokines, such as interferon-γ produced by T cells that have been attracted to the gland. Therefore, a T-cell receptor recognizes thyroid antigens on the surface of thyroid follicular cells, which are presented in the binding pocket of the HLA molecule [22]. These activated T cells act as helper cells that activate the B cells to secrete autoantibodies. Both of our patients had the HLA-DRB1 haplotype. However, studies in transgenic mice [5] and monozygotic twins [23] have shown that the expression of certain HLA molecules on thyrocytes or the genetic background in general is not sufficient to initiate the GD and probably environmental factors are required. Such factors as infections, life stress, iodine intake, smoking radiation and environmental toxicants have been proposed for the initiation of the autoimmune thyroid disease [24].

In recent years, Tg has been highlighted as the domain autoantigen in thyroid autoimmunity [9]. Iodinated peptides in Tg as well as iodine-induced apoptosis/necrosis of thyrocytes trigger autoimmune thyroid disease [25]. Increased release of Tg temporarily increases anti-Tg level, and has been reported after thyroid surgery [26], RAI administration [27], and ethanol administration in toxic adenomas [28,29]. In our cases, during the acute phase of SAT, serum Tg levels were increased, whereas anti-Tg was normal, which was followed by development of increased anti-Tg levels 3 months later, with the appearance of GD. It is possible that the release of Tg was the trigger for initiation of the autoimmune cascade. A limitation of our study is that we did not measure TSH receptor antibodies. However GD was confirmed by the combination of clinical and biochemical hyperthyroidism, positive anti-TPO and anti-Tg as well as high diffuse uptake of enlarged thyroid gland after scintigraphy with 5 µCi <sup>131</sup>I.

Our patients had the appropriate genetic background to develop either SAT or GD. We hypothesize that the genetic background and the increased load of Tg or other autoantigens released from the damaged thyroid gland due to SAT initiated the loss of immunological tolerance to thyroid antigens and cause the development of mild GD a few months later.

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