

Hashimoto's Thyroiditis Following Graves' Disease

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ABSTRACT

Both Graves' disease and chronic thyroiditis (Hashimoto's thyroiditis) are autoimmune diseases of thyroid gland. Graves' disease is caused by stimulation of TSH receptor located on the thyroid gland by an antibody, which is known as TSH receptor antibody (TRAb). Furthermore, this may lead to hyperplasia and hyperfunction of the thyroid gland. On the contrary, the cause of Hashimoto's thyroiditis is thought due to a TSH stimulation-blocking antibody (TSBAb) which blocks the action of TSH hormone and subsequently brings damage and atrophy to thyroid gland. Approximately 15-20% of patients with Graves' disease had been reported to have spontaneous hypothyroidism resulting from the chronic thyroiditis (Hashimoto's disease). Pathogenesis for chronic thyroiditis following anti-thyroid drug treatment in patients with Graves' disease remains unclear.

It has been estimated that chronic thyroiditis or Hashimoto's disease, which occurs following the Graves' disease episode is due to extended immune response in Graves' disease. It includes the immune response to endogenous thyroid antigens, i.e. thyroid peroxidase and thyroglobulin, which may enhance lymphocyte infiltration and finally causes Hashimoto's thyroiditis.

We report four cases of chronic thyroiditis (Hashimoto's disease) in patients who have been previously diagnosed with Graves' hyperthyroidism. In three cases, Hashimoto's thyroiditis occurs in 7 to 25 years after the treatment of Graves' disease; while the other case has it only after few months of Graves' disease treatment. The diagnosis of Hashimoto's disease (chronic thyroiditis) was based on clinical manifestation, high TSHs level, positive thyroid peroxidase antibody and thyroglobulin antibody, and supported by positive results of fine needle aspiration biopsy. Moreover, the result of histopathological test has also confirmed the diagnosis in two cases. All cases have been successfully treated by levothyroxine treatment.

Key words: hashimoto's thyroiditis, graves' disease, TSH receptor antibody (TRAb), TSH stimulation on-blocking antibody (SSBAb).

INTRODUCTION

Graves' disease and Hashimoto's disease (chronic thyroiditis) are thyroid autoimmune diseases. Graves' disease is caused by stimulation of TSH receptor located on the thyroid gland by an antibody, which is known as TSH receptor antibody (TRAb). Furthermore, this may lead to hyperplasia and hyperfunction of the thyroid gland. On the contrary, the cause of Hashimoto's thyroiditis is thought due to a TSH stimulation-blocking antibody (TSBAb) which blocks the action of TSH hormone and subsequently brings damage and atrophy to thyroid gland.^{1,2} In patients with Graves' hyperthyroidism, after 10-15 years discontinuation of antithyroid treatment or following the subtotal thyroidectomy; about 15-20% had been reported to develop spontaneous hypothyroidism due to Hashimoto thyroiditis.³⁻⁵

Anti-thyroid treatment may lower the TRAb level; however, in patients who have both stimulating and blocking antibody, decreased TRAb level will increase the action of TSBAb, which eventually causes Hashimoto's thyroiditis.⁶ The development of Hashimoto's thyroiditis following Graves' disease is rarely reported. Welsum et al⁷ reported 15 cases of Hashimoto's thyroiditis in patients with Graves' disease 20 to 27 years following thyroidectomy procedures. Wood et al⁴ reported 15 cases of hypothyroidism in patients with Graves' disease 20-27 years after discontinuation of anti-thyroid treatment. Moreover, 80% of them have positive microsomal antibody test indicating the occurrence of autoimmune hypothyroidism.

No report in the literature has been found in Indonesia regarding the incidence of Hashimoto's thyroiditis in patients with Graves' disease. We report four cases which were previously diagnosed as Graves' hyperthyroidism, but developed further into Hashimoto's thyroiditis after being treated with anti-thyroid drugs.

CASE ILLUSTRATION

Case 1

A 33-year-old woman, YI, was seen in January 1992 complaining of clinical hyperthyroidism manifestation, i.e. weight loss, excessive sweating, palpitation, diffuse thyroid enlargement. No abnormality found in eyes examination. The result of thyroid function, FT4 was 5.1 ng/dL (normal = 0.68 – 1.76 ng/dL) and TSHs was < 0.005 (normal = 0.1 – 5.0 μ IU/mL). The patient was begun on propylthiouracil (PTU) 3 x 100 mg/day and the dose was lowered to 100 mg/day for 2 year which then discontinued after the results of FT4 and TSHs have been repeatedly within the normal limit. Eight months after discontinuation of PTU, the patient had another visit and complained of excessive sweating and palpitation. The thyroid function test revealed that FT4 was 3.63 (normal 0.68-1.76 ng/dL) and TSHs was 0.07 μ IU/mL (normal 0.1- 5.0 μ IU/mL). Afterward, the patient had another course of PTU treatment at 100 mg/day. PTU treatment was continued until 2002.

In 2003, the patient had another visit and complained of early fatigue and neck enlargement. On physical examination, the a diffuse thyroid enlargement was found, the TSHs was 10.9 μ IU/mL (normal 0.4 – 4.0 μ IU/mL) and FT4 was 0.5 ng/dL (normal 0.68 – 1.76 ng/dL). The antibody test was performed, revealing positive AMA test of 1:10.400 and anti-thyroglobulin of 1:5120. Fine needle aspiration biopsy found numerous lymphocytic infiltration and Askanazy cells. The current diagnosis is Hashimoto's disease or chronic thyroiditis. The patient is has being treated with Thyrax at dose of 100 ug/day until now and she is in a good condition. The final diagnosis is Graves' disease preceeding Hashimoto's disease.

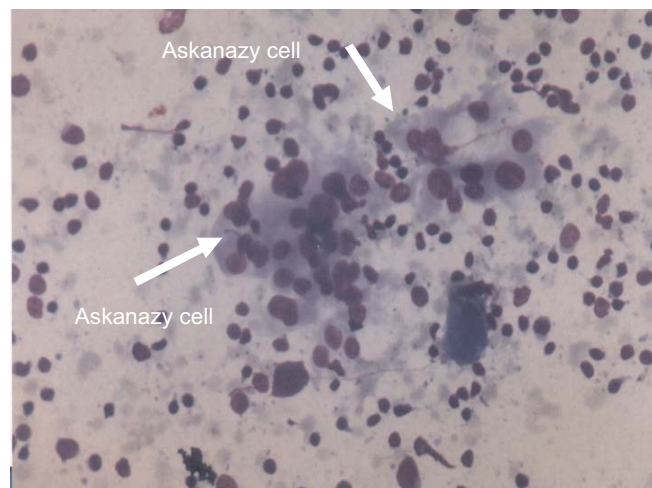


Figure 1.

Case 2

A 32-year-old man, TA, was referred in December 2006 with enlargement of thyroid gland. Based on history, the patient had 12 kg weight loss in three months period of time, excessive sweating, early fatigue and short of breath when he walked. The family history revealed that his younger sister had toxic goiter (thyrotoxicosis) and had long-term PTU treatment. On examination, there was diffuse thyroid enlargement. No eyes abnormality was present. He has already had laboratory results, which revealed FT4 of > 6.00 ng/dL. The patient was treated with Thyrozole^o 3 x 10 mg/day.

After seven-month treatment, in June 2007, the patient came back and complained of a greatly enlarged neck, fatigue and choking episodes. On examination, the thyroid gland has greater diffuse enlargement than previous one. The thyroid function included FT4 was 0.476 ng/dL (normal: 0.7 – 1.78 ng/dL), and TSHs was > 60 μ IU/mL (normal: 0.4 – 6.2 μ IU/mL). The antibody test revealed AMA 1: 6.400. Fine needle aspiration biopsy found numerous lymphocytic infiltration and Askanazy cells, which was compatible with Hashimoto's thyroiditis. After being treated with three-month Euthyrox treatment at dose of 1 x 100 μ g/day, the neck enlargement was persistent. Therefore, thyroidectomy was performed by surgeons in April 2004 since the very large goiter has caused compression on other structures.

The result of pathology anatomy examination provided evidence on Hashimoto's thyroiditis. Euthyrox has being continued until now (2009) at dose of 1 x 100 μ g/day. The final diagnosis is Graves' disease preceeding Hashimoto's thyroiditis.

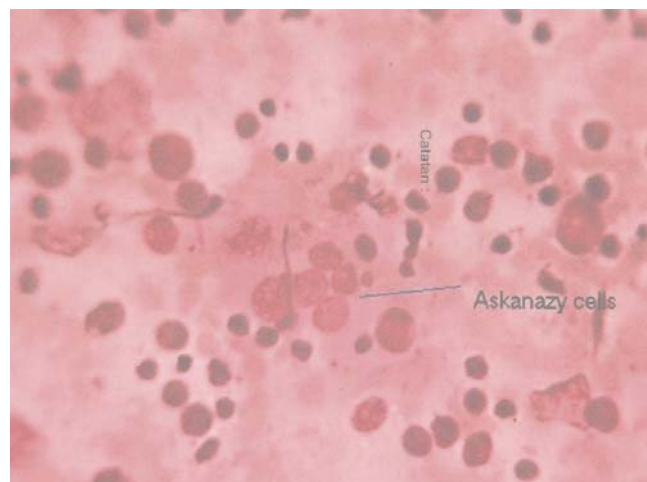


Figure 2.

Case 3

A 25-year-old woman, RO, came in August 2002 with complaints of neck enlargement, which has occurred for several months, 6 kg weight loss, excessive sweating and early fatigue. On physical examination, we found periorbital edema with class 1 impression, diffuse thyroid enlargement, and tremor was present in both hands. The thyroid function test revealed that FT4 was 2.47 ng/dL (normal: 0.7 -1.78 ng/dL), TSHs was <0.01 μ IU/mL (normal: 0.4 - 4 μ IU/mL). The diagnosis was Graves hyperthyroidism and she was treated with Neomercazole 10 mg/day. Due to incompliance of irregular treatment, Neomercazole was taken only until April 2006, and then the treatment was discontinued. In November 2006, the patient had another visit and complained of palpitation, excessive sweating and the thyroid function revealed that FT4 was 5.2 ng/dL (normal: 0.2 – 2.0 ng/dL), TSHs was 0.1 μ IU/mL (normal: 0.4 – 6.2 μ IU/mL). She was then treated with Thyrozole 2 x 10 mg/day. The patient had regular treatment and her thyroid function was within the normal limit.

In February 2009, surgical treatment was selected by the patient as she felt further enlargement of thyroid gland and choking episodes. The pre-surgical chest X ray revealed intrathoracic thyroid glands. Pre-surgical laboratory test revealed FT4 was 1.3 ng/dL (normal: 0.8 – 1.8 ng/dL), TSHs was 0.281 μ IU/mL (normal: 0.4 – 4.0 μ IU/mL), and other laboratory parameters were within the normal limit. A subtotal thyroidectomy was

performed in February 2009. The result of pathology anatomy examination revealed several lymphoid follicles and lymphocytic infiltration, which was consistent with Hashimoto's thyroiditis. The result of post surgical antibody test was AMA test being 1: 400 and anti-thyroglobulin test was 1:40. The TSHs level after the surgery was 27.0 μ IU/ml (normal: 0.4-4.0 μ IU/mL, Calcium blood level was 6.8 mg/dL (normal: 8.1-10.14 mg/dL). The patient was further treated with Euthyrox 1 x 100 ug/day and Ca Sandoz 1000 mg/day. Her last visit was on April 16th 2009 with data of TSHs was 0.8 μ IU/mL (normal: 0.4 – 6.2 μ IU/mL), Ca blood level 9.2 mg/dL. The final diagnosis is Graves' disease preceding Hashimoto's thyroiditis and hypocalcemia.

Case 4

Mrs FA, a 49-year-old woman who has had Graves hyperthyroidism since 1974 and has received PTU treatment. In 1979, after she became euthyroid, a subtotal thyroidectomy was performed. The second surgery was performed in 1993 since there was a residue hyperthyroidism. In March 2005, the patient had another visit and brought her laboratory test results revealing TSHs of 21.2 μ IU/ml (normal: 0.4-4.0 μ IU/mL) and FT4 of 0.8 ng/dL (normal: 0.8 – 2.0 ng/dL).

In contrast to her previous condition, the patient more frequently has the feeling of cold, early fatigue, and slight increase in weight i.e. 3 kg in the last six months. The physical examination found a mass on the right neck region, at the size of pingpong ball and there was

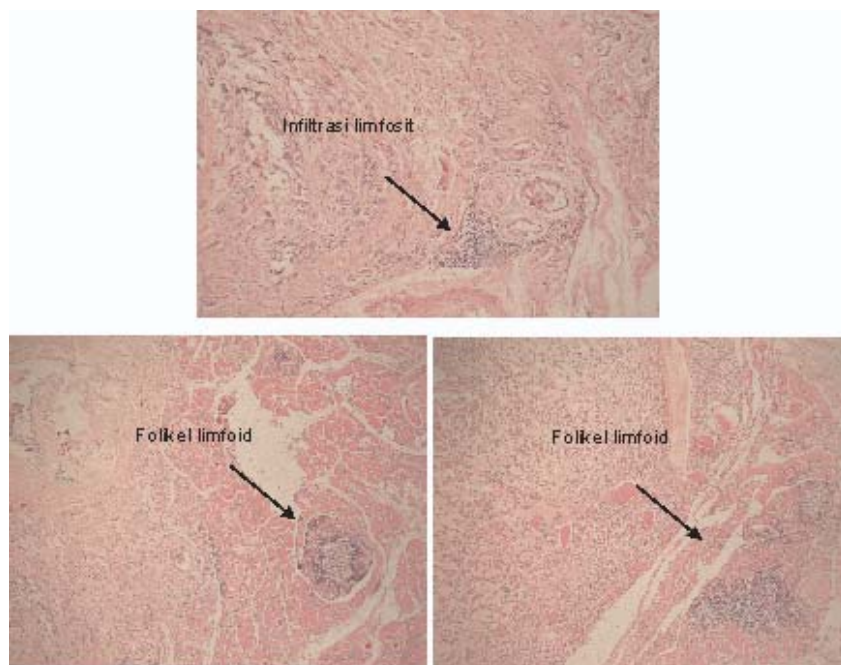


Figure 3.

cicatrix resulting from her previous surgery along her left and right neck. The thyroid function revealed that TSHs was 72.2 μ IU/mL (normal: 0.4-4.0 μ IU/mL), FT4 was 0.3 ng/dL (normal: 0.8 – 1.8 ng/dL). The microsomal antibody was 1: 6400, anti-thyroglobulin antibody was 1:320 and serum calcium level was 8.5 mg/dL (normal: 8.0 – 10.0 mg/dL). After having the patient's consent, fine needle aspiration biopsy was performed. It demonstrated numerous lymphocytes and several Azkanzy cells, which were compatible with Hashimoto's thyroiditis. The patient was then treated with Euthyrox 100 ug/day. The diagnosis is Hashimoto's thyroiditis following Graves hyperthyroidism.

DISCUSSION

Patients with Graves hyperthyroidism may experience persistent hypothyroidism following the thyroid surgery, which causes excessive removal of thyroid gland. Moreover, such hypothyroidism is most frequently caused by I¹³¹ treatment. About 15-20% patients with Graves' disease may have spontaneous hypothyroidism due to Hashimoto's thyroiditis, after discontinuation of anti-thyroid treatment.³⁻⁵ The pathogenesis of Hashimoto's thyroiditis in patients with Graves' disease has not been confirmed. Tamal⁸ suggested that pathogenesis of spontaneous hypothyroidism in patients with Graves' disease following the discontinuation of anti-thyroid may be caused by three mechanisms, i.e. a) the presence of autoimmune destruction that may cause high TRAb level and negative TSBAb level; b) diminished TRAb due to treatment and increased TSBAb, in other words, it is due to high level of blocking antibody; and c) the presence of focal thyroiditis.

The association between Graves' disease and Hashimoto's thyroiditis has been controversial for decades. At the beginning, they were regarded as two different disease entities. Most authors assume that Hashimoto's disease (chronic thyroiditis) as part of Graves' disease since both diseases occur concomitantly, which is known as concomitant chronic thyroiditis. Recent view considers that both diseases exemplify two sides of the same coin.⁴

McLachlan SM regards that the existence of Hashimoto's thyroiditis following the Graves' disease is attached to immune mechanism, i.e. a tolerance system which is a complex process involving central and peripheral mechanism for eliminating self-reactive lymphocytes. In addition, the role of regulatory T cells (CD4, CD25 or CD28 CD122 of T cells) which organize the autoreactive effector of T cells in the peripheral area has also been emphasized. Thyroid stimulating autoantibody is produced

due to damage on self-tolerance towards TSHR leading to the development of Graves disease. Autoantigen that induce immune response in Graves' is subunit A, which is an ecto-domain component detached following intramolecular fragmentation of a receptor. Furthermore, there is expansion of immune response toward endogenous thyroid antigen, i.e. the thyroid peroxidase and thyroglobulin which consequently cause extensive lymphocytic infiltration leading to Hashimoto's thyroiditis.⁹

Regulatory T cells (Treg) is a major factor in intermolecular immune response expansion, both from TSHR to TPO and Tg and alteration of hyperthyroid into Hashimoto's thyroiditis with massive thyroid lymphocytic infiltration, which causes hypothyroid state.⁹

All four cases reported here obviously are Hashimoto's thyroiditis or chronic thyroiditis as indicated by high TSHs level, which points to hypothyroidism and high microsomal and thyroglobulin antibody level denoting the autoimmune process of Hashimoto's thyroiditis. It has been known that anti-microsomal antibody is found in 95% cases of Hashimoto's thyroiditis; while antithyroglobulin is found in 60% cases.¹⁰ Diagnosis of Hashimoto's thyroiditis can be made only based on clinical manifestation of hypothyroidism along with high TSHs level, as well as some tests on the occurrence of antimicrosomal antibody (AMA) and thyroglobulin antibody. Most patients with Hashimoto's thyroiditis present with diffuse thyroid enlargement; and only about 10% who present without thyroid enlargement, known as the atrophic form. Therefore, cytological examination of fine needle aspiration biopsy is only necessary in an uncertain cases.²

The first case demonstrates clinical manifestations and laboratory results which comply with Graves' hyperthyroidism. Relapse of hyperthyroidism or recidive hyperthyroidism occurs after anti-thyroid treatment has been discontinued for several times. Hashimoto thyroiditis in this patient was confirmed by positive microsomal antibody and antithyroglobulin titer and supported by fine needle aspiration biopsy.

In the second case, hypothyroidism developed in only 7 months after diagnosis of Graves' hyperthyroidism was established. To our knowledge, clinical manifestation of Hashimoto's thyroiditis may take place through three stages, i.e. the early stage, second and final stage. The early stage has hyperthyroidism state as there is excessive thyroid hormone secretion into circulation due to partial destruction thyroid cells. In the second stage, the thyroid has normal function (euthyroid) and the final stage includes hypothyroidism. Hashimoto's hyperthyroidism usually has mild and transient hyperthyroidism;

thus, most patients in hyperthyroid state remain unrecognized. In this patient, the clinical manifestations and very high level of FT4 suggesting Graves' hyperthyroidism; however, there was no TRAb results to confirm such a diagnosis. Nevertheless, in addition to high TSHs level, positive microsomal antibody and thyroglobulin antibody as well as the result of histopathological examination have provided evidences for Hashimoto's thyroiditis.

The third case illustrates a patient who was hospitalized due to Graves' hyperthyroidism. He had classic clinical manifestations along with ophthalmopathy, high FT4 level and low TSHs level. The patient has been treated for seven years with anti-thyroid, Thyrozole; and subsequently, he asked for surgical treatment. The indication for surgical removal was due to greatly enlarged thyroid gland, which caused choking episodes plus the patient had been in euthyroid state. A subtotal thyroidectomy was then performed. Histopathological results following the surgery indicates Hashimoto's thyroiditis. Microsomal antibody and thyroglobulin antibody tests also revealed positive results.

The fourth case describes a patient who has already had treatment for Graves' hyperthyroidism and had undergone two times surgery; the last surgery was due to recidive hyperthyroidism. Over a 12-year period following the surgery (2005), her laboratory result indicated subclinical hypothyroid state. Four years later, she came for another visit and her laboratory results suggested hypothyroid state as indicated by high TSHs level, positive microsomal antibody and thyroglobulin antibody in addition to the result of fine needle aspiration biopsy that demonstrated numerous lymphocytes and some Azkanazy cells which were appropriate to Hashimoto's thyroiditis.

The abovementioned cases obviously suggest diagnosis of Hashimoto's hyperthyroiditis following Graves' hyperthyroidism. In the first, third and fourth cases, Hashimoto's thyroiditis has only been diagnosed after a quite long period of time since the previous diagnosis of Graves' hyperthyroidism had been established (10, 7 and 25 years, respectively). Such conditions are similar to other studies, the diagnosis were made in 10 to 20 years of time after discontinuation of anti-thyroid drugs.^{4,7}

In those four cases, we assume that the mechanism contributing to the development of Hashimoto's thyroiditis is due to expansion of immune response, i.e. an autoimmune process that stimulates the TSH receptor; in this case, TRAb to produce autoantibodies toward thyroid peroxidase (TPO) and thyroglobulin (Tg). We propose such mechanism since in those cases, no

examination on TRAb or TSBAb has been conducted at the beginning stage of Graves' disease to confirm concurrence of both diseases.

CONCLUSION

Both Graves' hyperthyroidism and Hashimoto's thyroiditis are thyroid autoimmune disease. In 10 to 15% of Graves' hyperthyroidism cases, Hashimoto's thyroiditis may occur after remission by anti-thyroid treatment. We assume that it is due to the expansion of immune response of autoantibodies that stimulate TSH receptor. Subsequently, it produces autoantibodies against TPO and TG causing lymphocytic infiltration and defect on thyroid cells; finally, hypothyroid occurs. We suggest continuous monitoring of thyroid function in patients with Graves' disease in spite of remission after being treated with anti-thyroid agents.

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