Hashimoto Auto-immune Tyroiditis with Different Clinical Manifestations

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In the year 1912, Hashimoto first reported four women with diffuse struma which under anatomic pathology demonstrated four unique findings of diffuse lymphocyte infiltration, the formation of lymphoid follicles, destruction of thyroid epithelial cells, and formation of fibrous tissue; thus called lymphomatous struma.[1,2] Forty years later, an anti-thyroid antibody was found in the serum of the patients introduced by Hashimoto. Since then, clinical conditions of diffuse struma with the presence of anti-thyroid antibodies are known as Hashimoto disease, or Hashimoto autoimmune thyroiditis.[1]

With further developments, there were many diseases with the same histological findings, and the presence of anti-thyroid antibodies are not always associated with diffuse struma such as that in the classical Hashimoto disease. Thus, the more common name used nowadays is chronic autoimmune thyroiditis. Clinically, chronic autoimmune thyroiditis is classified into two forms, first with diffuse enlargement of the thyroid gland (goitrous form) known as Hashimoto disease or Hashimoto autoimmune thyroiditis, and the second without thyroid gland enlargement, known as chronic atrophic thyroiditis.[1,2,3]

The incidence rate of Hashimoto autoimmune thyroiditis is quite high and has a tendency to increase in uncertain numbers. The average incidence rate is 3.5 cases in 1000 females and 0.8 cases in 1000 males.[4] The prevalence of chronic autoimmune thyroiditis in Western countries such as the United States and the United Kingdom was reported to be 5-15% in females and 1-5% in males.[1] In Indonesia, cases of Hashimoto autoimmune thyroiditis cases are very rare. A histopathological examination analysis of thyroid operation cases in Surabaya for 2 years only found 28 cases of Hashimoto autoimmune thyroiditis out of 2185 thyroid specimens, or 1.3%,[5] while data from the Department of Pathologic Anatomy of the Faculty of Medicine of Hasanuddin University found 3 cases of Hashimoto autoimmune thyroiditis out of all thyroid samples in 3 years.[6]

A diagnosis of Hashimoto autoimmune thyroiditis should always be considered when finding patients with diffuse struma with or without complaints or clinical signs of hypothyroidism, accompanied by increased levels of serum thyrothropine (thyroid stimulating hormone = TSH). Increased levels of one of the anti-thyroid antibodies, such as the anti-microsomal antibody (AMA), anti-thyroid peroxidase antibody (anti-TPO), or anti-thyroglobulin (anti-Tg) are needed to prove the presence of an autoimmune process. Histopathological or cytological examination would further support the diagnosis of Hashimoto autoimmune thyroiditis.[3,4]

Thyroid dysfunction in Hashimoto autoimmune thyroiditis can take the form of normal thyroid function (euthyroid), hypothyroidism, or transient hyperthyroidism.[2,3,4] Most patients manifest as hypothyroidism, but hypothyroidism with classical clinical findings (overt hypothyroidism) is only reported in 10% of cases. Hashimoto autoimmune thyroiditis may demonstrate mild to severe manifestations.[2] We hereby report three cases of Hashimoto autoimmune thyroiditis with different clinical manifestations.

CASE REPORT

Case 1

A 35 year-old male came to the Internal Medicine Out-patient Clinic with a chief complaint of enlargement in the neck. The patient had only realized his condition 1 week prior to his visit, followed by a feeling of strangulation, without disturbance in swallowing or pain. The patient also complained of feeling cold, easily fatigued, and reduced sweating. There was no history of fever.

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The patient did not feel any weight change, hair loss, difficulty breathing, or palpitations. There was no family history of goiter disease.

During physical examination, the patient appeared healthy and fully conscious. He weighed 66 kg and was 165 cm in height. His blood pressure was 110/70 mmHg, his pulse rate 72 times per minute, his respiratory rate 20 times per minute, and there was no fever. His eyes were not protruded, his conjunctiva normal, his sclera showed no signs of jaundice. There was no lymph gland enlargement in the neck. There was diffuse thyroid gland enlargement, supple in consistency, moves along when swallowing, with a smooth surface and no tenderness. The neck circumference was 39 cm. There was no thyroid murmur nor stridor. The chest was normal in shape and symmetrical. The patient's lungs were normal, no rales were found. The patient's heart was within normal limits, no murmur was found. The patient's abdomen was not distended and there was no ascites. The patient's liver and spleen were not palpable, and his bowel sounds were normal. There was no edema of the extremities, the skin was normal and smooth.

Laboratory results on October 26th, 2000 were as follows: Hemoglobin level 14 g%, white blood cell count 9,200/mm3, blood sedimentation rate 40 mm/hour. Routine urinalysis results were normal. Liver and renal functions were within normal limits. The patient's total cholesterol was 314 mg/dl, LDL-cholesterol 242 mg/dl, HDL-cholesterol 27 mg/dl, triglyceride 225 mg/dl. Thyroid function examination demonstrated thyrothropine (TSH-sensitive) levels of >100 uIU/ml (normal levels 0.3 uUI/ml). Electrocardiogram demonstrated normal findings. The results of thyroid ultrasonography demonstrated diffuse thyroid gland enlargement with a low echo rate, in accordance with thyroiditis. Based on a history of enlargement of the thyroid gland accompanied by a sense of strangulation, a feeling of coldness, decreased sweating, and easy fatigue, without disturbance in swallowing or breathing, or pain; a physical evaluation demonstrating diffuse struma; and an ultrasound examination demonstrating diffuse struma in accordance with thyroiditis with elevated thyrotropine levels; the current working diagnosis is a suspicion of Hashimoto autoimmune thyroiditis with a manifestation of hypothyroidism. The differential diagnosis is "silent thyroiditis". The patient received 100 ug/day of Euthyrox (levothyroxine) and vitamins.

The results of the antimicrosomal antibody examination on November 4th 2000 demonstrated a very high titer of 1:24,6000 (normal: negative). Fine needle aspiration biopsy results on November 18th 2000 demonstrated that the two samples from the left and right thyroid glands were full of lymphocyte cells. The conclusion was lymphocytic thyroiditis (Figure 1). The results of the antimicrosomal antithyroid antibody (AMA) and fine needle aspiration biopsy were in accordance with lymphocitic thyroiditis, thus supporting the diagnosis of Hashimoto autoimmune thyroiditis with a manifestation of hypothyroidism.

After treatment with 100 ug of Euthyrox daily for 2 months, the thyrotropine levels at 2 months follow-up was still a high 67.49 uIU/ml (normal: 0.3-5 uUI/ml). Nevertheless, the feelings of strangulation, coldness, and decreased sweat were reduced. The patient's neck diameter dropped to 37 cm. Because of the high thyrothropine levels, the dose of Euthyrox was increased to 150 ug/day. Six months later, the level of thyrothropine had reached 7.9 ul/ml, while the AMA titer remained at 1:25,600. The patient felt better. Six months later, the patient returned with fatigue and a cold feeling. Based on history, the patient had stopped taking Euthyrox for 2 months. The patient's TSH level had increased to over 75 ul/ml. Treatment with 150 ug/day of Euthyrox was continued.

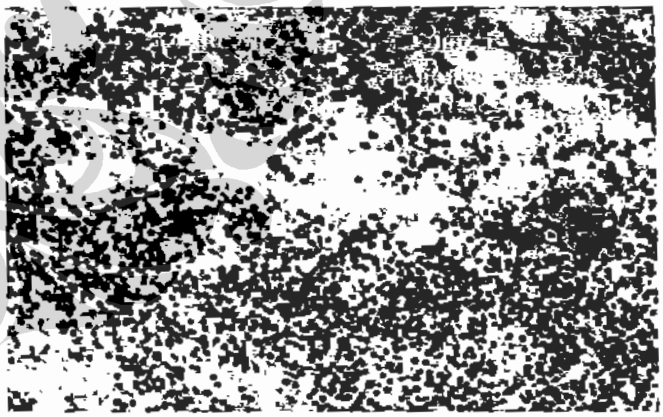

Figure 1. The Cytological Findings from Fine Needle Aspiration Biopsy of Case 1 Patient

Case 2

A 24 year-old female came to the Internal Medicine Out-patient Clinic of Jaury Academic Hospital with a chief complaint of enlargement of the neck. The patient had only realized her condition in less than 1 week. The patient did not report pain, a sense of strangulation, difficulty breathing or swallowing. There was no prior history of fever, weight change, hair loss, difficulty breathing, cold sensation, or palpitations. There was no family history of goiter disease.

During physical examination, the patient appeared healthy and fully conscious. She weighed 53 kg and was 154 cm in height. Her blood pressure was 110/70 mmHg, her pulse rate 80 times per minute, her respiratory rate 20 times per minute, and there was no fever. Her eyes were not protruded, her conjunctiva not anemic, her sclera showed no signs of jaundice, and there was no edema of the eyelids. There was no lymph gland enlargement in the neck. There was diffuse thyroid gland enlargement, supple in consistency, moves along when swallowing, with a smooth surface and no tenderness. There was no thyroid murmur or stridor. Her neck circumference was 33 cm. The chest was normal in shape and symmetrical. The patient's lungs were normal, no rales were found. The patient's heart was within normal limits, no murmur was found. The patient's abdomen was not distended and there was no ascites. The patient's liver and spleen were not palpable, and his bowel sounds were normal. There was no edema of the extremities, the skin was normal and smooth.

Laboratory results on May 11th, 2001 were as follows: Hemoglobin level 13 g%, white blood cell count 7000/mm3, blood sedimentation rate 69 mm/hour. Routine urinalysis results were normal. Thyroid function examination demonstrated thyrothropine levels of 2.74 uIU/ml (normal levels 0.3-5 uUI/ml). Assessment for AMA turned out negative (normal). Electrocardiogram demonstrated sinus rhythm. The results of thyroid ultrasound examination demonstrated diffuse thyroid gland enlargement with a low echo rate, in accordance with thyroiditis. Fine needle aspiration biopsy gave the impression of a benign process possibly being colloid struma. Based on a history of enlargement of the thyroid gland without pain, a sense of strangulation, a feeling of coldness, decreased sweating, and easy fatigue, or a disturbance in swallowing or breathing; a physical evaluation demonstrating diffuse struma; and an ultrasound examination demonstrating diffuse struma in accordance with thyroiditis without increased thyrotropine levels; the working diagnosis at the time was non-toxic diffuse struma. The differential diagnosis was Hashimoto autoimmune thyroiditis or "silent thyroiditis". The patient was only given vitamins.

Nine months later (on February 6th 2002), the patient returned for control. At this point, the patient complained of enlargement of the neck and a sense of strangulation. During palpation, there was diffuse thyroid gland enlargement, supple in consistency, moves along when swallowing, with a smooth surface and no pain. There was no thyroid murmur or stridor. The patient's neck circumference was increased to 35.5 cm. Other physical examination gave a normal impression. Repeat assessment of thyrothropin levels resulted in 18.6 uIU/ml (normal: 0.3-5 uIU/ml). FT 0.25 ng/ml (normal: 0.71-1.85 ng/ml). AMA results were still negative, but the patient's anti-Tg antibody titer was over 300 ng/ml (normal: <55 ng/ml). Thyroid ultrasound control examination gave the same impression, diffuse thyroid gland enlargement with low echo levels in accordance with thyroiditis.

The second fine-needle biopsy aspiration found a smear filled with many follicles distributed with many mature lymphocytes in the background, giving the impression of a lymphocytic thyroiditis (Figure 2). Based on a history of enlargement on the neck, physical examination of a diffuse struma, increased thyrothropine and anti-Tg antibody levels, and fine needle biopsy aspiration findings of lymphocytic thyroiditis, the diagnosis in this patient was Hashimoto autoimmune thyroiditis with a manifestation of hypothyroidism. The patient was given 100 ug Euthyrox daily.

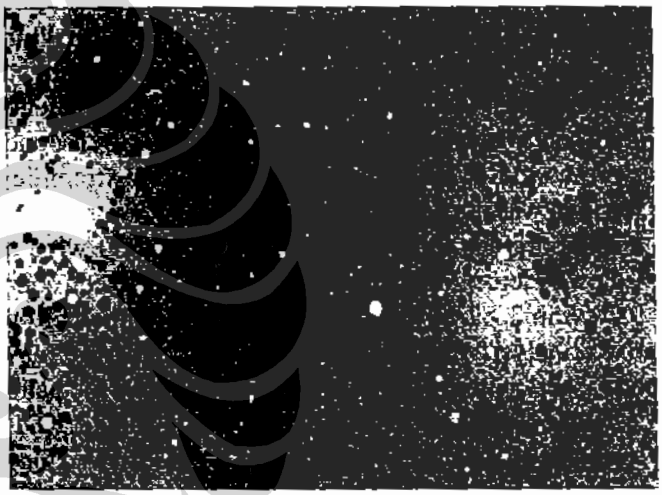

Figure 2. Cytological Results of Fine Needle Aspiration Biopsy of Patient in Case 2

Case 3

A 53 year-old female came with a chief complaint of enlargement of the neck. The patient realized her condition since 2 weeks prior to the visit. The patient did not report a sense of strangulation, difficulty in breathing or swallowing, or pain. There was no prior history of fever, weight change, hair loss, difficulty breathing, cold sensation, or palpitations. There was no family history of goiter disease.

In 1997, the patient had suffered the same complaint, with enlargement of the neck, feeling easily fatigued and always feeling cold. Her thyroid function at the time

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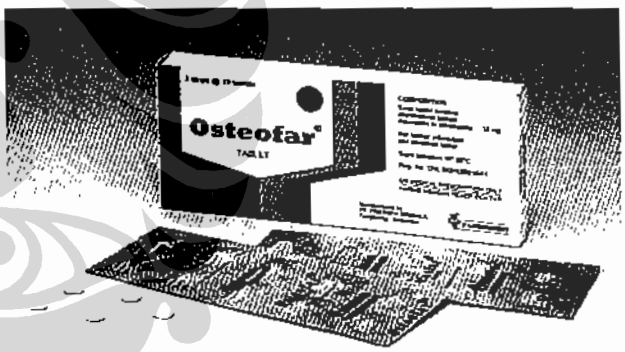

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(thyrothropine level) was 46.19 uIU/ml (normal: 0.3-5 uIU/ml), while her AMA was positive with a titer of 1:6400 (normal: negative), and her anti-Tg antibody negative. She received 100 ug of Euthyrox daily for 6 months. The patient never came for follow-up since she had felt better (her neck enlargement reduced in size).

During physical examination on December 20th, 2001, the patient appeared healthy and fully conscious. She weighed 59 kg and was 163 cm in height. Her blood pressure was 120/80 mmHg, her pulse rate 80 times per minute, her respiratory rate 20 times per minute, and there was no fever. Her eyes were not protruded, her conjunctiva not anemic, her sclera showed no signs of jaundice, and there was no edema of the eyelids. There was no lymph gland enlargement in the neck. There was diffuse thyroid gland enlargement, supple in consistency, moves along when swallowing, with a smooth surface and no tenderness. There was no thyroid murmur or stridor. Her neck circumference was 35.5 cm. The chest was normal in shape and symmetrical. The patient's lungs were normal, no rales were found. The patient's heart was within normal limits, no murmur was found. The patient's abdomen was not distended and there was no ascites. The patient's liver and spleen were not palpable, and his bowel sounds were normal. There was no edema of the extremities, the skin was normal and smooth.

Laboratory results on December 21st, 2001 were as follows: Hemoglobin level 13.8 g%, white blood cell count 5300/mm3, blood sedimentation rate 26 mm/hour. Routine urinalysis results were normal. The patient's total cholesterol was 275 mg/dl, LDL-cholesterol 177 mg/dl, HDL-cholesterol 58 mg/dl, triglyceride 66 mg/dl. Thyroid function examination demonstrated a thyrothropine level of > 75 uIU/ml (normal levels 0.3-5 uUI/ml), FT 1.2 ng/ml (normal: 0.71-1.85 ng/ml). Assessment for AMA turned out positive with a titer of 1:1600 (normal: negative). Electrocardiogram demonstrated sinus rhythm and a complete right bundle branch block. The results of thyroid ultrasound examination demonstrated diffuse thyroid gland enlargement with a low echo rate, in accordance with thyroiditis.

Fine needle aspiration biopsy on December 24th, 2001 resulted in a smear of follicle cells, plenty of Azkanazy cells, and lymphocyte cells, with the impression of Hashimoto struma (Figure 3). Based on a history of enlargement of the thyroid gland and a history of Hashimoto autoimmune thyroiditis, a physical evaluation demonstrating diffuse struma, an ultrasound examination demonstrating diffuse struma in accordance with thyroiditis, increased thyrotropine levels, a positive AMA, and fine needle aspiration biopsy in accordance with Hashimoto autoimmne thyroiditis, the working diagnosis was Hashimoto autoimmune thyroiditis with a manifestation of hypothyroidism. The patient received 100 ug of Euthyrox daily.

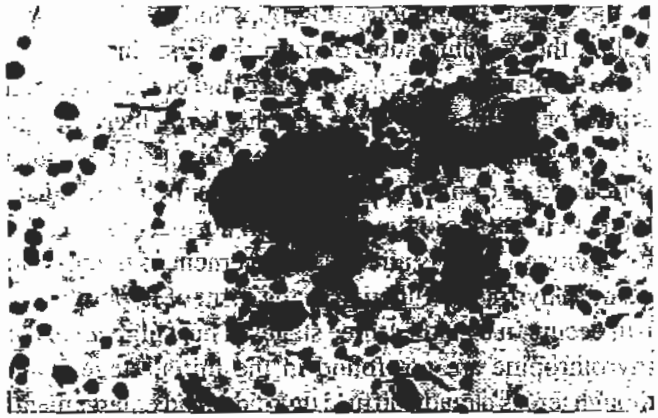

Figure 3. Cytological Results of Fine Needle Aspiration Biopsy of Patient in Case 3

DISCUSSION

Chronic autoimmune thyroiditis is classified into Hashimoto autoimmune thyroiditis accompanied by thyroid gland enlargement, which is the most common case; and atrophic autoimmune thyroiditis, without thyroid gland enlargement.[1,2,7] Indonesian literature reported very few cases of Hashimoto thyroiditis, only 3 in the record.[6,8,9] This may be because there are not many cases of Hashimoto autoimmune thyroiditis, or because cases were missed, thus complete evaluation was not conducted, particularly thyroid antibody evaluation to diagnose this disease. Bearing in mind that most patients do not demonstrate classical thyroid dysfunction such as hypothyroidism,[1,2,3,4] the diagnosis of Hashimoto autoimmune thyroiditis should be considered when encountering an adult patient with diffuse struma and high TSH levels.[1,4,7] To prove the presence of an autoimmune process, anti-thyroid antibody such as anti-microsomal antibody or anti-thyroglobulin should be assessed.[1,3,4] Unfortunately, aside from the relatively high cost of anti-thyroid antibody evaluation, the test might not be available at local laboratories (samples need to be sent to Jakarta).

Amino and Tada[2] classified the manifestations of Hashimoto autoimmune thyroiditis into four subgroups according to the manifestation stage of the disease: the early stage, called the subclinical subgroup; the mild stage, called the chronic subgroup; the advanced stage, which

is the classic Hashimoto subgroup; and the final stage, called the atrophic subgroup. In the first three forms, there is enlargement of the thyroid gland of varying sizes, while for the final form, the atrophic form, there was no thyroid gland enlargement. Thyroid function depended on the stage of manifestation. In the subclinical stage, the patient's thyroid function is still normal (euthyroid), even though there is already enlargement of the thyroid gland. Thyroid dysfunction in the form of hypothyroidism occurs in the other three stages. Thus, high levels of thyrothropine are not found in the initial stage, even though tere is already diffuse thyroid gland enlargement. This shows that during the initial stage, there is not much damage of thyroid cells, thus maintaining thyrothropine levels within normal limits.[2,3,10]

Cases 1 and 3 can be classified as the classical form of Hashimoto autoimmune thyroiditis due to findings of diffuse struma, high levels of AMA, and increased thyrothropin levels, even though there were no classical clinical findings of hypothyroidism. Case 2 initially can be classified as the subclinical form of Hashimoto autoimmune thyroiditis due to normal levels of thyrothropine hormone, which then became the chronic form, proven with increased thyrothropine levels.

Administration of thyroxin in patients with Hashimoto autoimmune thyroiditis is determined by thyroid function. In cases of definite clinical hypothyroidism, thyroxin has to be administered.[1,2,3] The administration of thyroxin in cases of euthyroid and subclinical hypothyroid Hashimoto autoimmune thyroiditis is still controversial. Lamberton and Jackson 3 recommend the administration of thyroxin in cases of euthyroid with the argument that it could reduce the size or suppress enlargement of the thyroid gland. According to Dayan[1] in subclinical hypothyroidism, new thyroxin is only administered after the thyrothropin level exceeds 10 mU/L. Thyroxin administration in cases of Hashimoto autoimmune thyroiditis with hypothyroidism has three benefits as follows: a) as a hormone supplementation due to inadequate thyroid hormone deficiency, b) thyroxin reduces thyrothropine levels to reduce the size of the thyroid gland, and c) thyroxin is suspected to be able to suppress the autoimmune process in the thyroid, thus causing remission, as proven from the reduction of antimytochondria antibody (AMA) levels.[11,12]

Approximately 20%of patients with Hashimoto autoimmune thyroiditis may achieve remission after the administration of thyroxin for several months to one year.[3] Takasu reported 20% remission in 92 patients with Hashimoto autoimmune thyroiditis receiving only 1 year of thyroxin. The third case presented in this paper also demonstrated the possibility that thyroxin had achieved temporary remission and recurrence after 4 years, even though this is only based on history of alleviation of complaints and reduction in the size of the thyroid gland.

Hashimoto autoimmune thyroiditis may take the form of mild to severe hypothyroidism. The first case reported demonstrated classical findings of Hashimoto autoimmune thyroiditis. The second case was in accordance with the initial stage of Hashimoto autoimmune thyroiditis with normal levels of thyrothropin, then becoming mild stage with increased levels of thyrothropin. The third case is a case of remission after thyroxin, which then recurred after 4 years.

SUGGESTION

All patients with diffuse struma with or without an unclear etiology with or without increased levels of thyrothropin should undergo anti-thyroid antibody assessments, particularly that of anti-microsomal antibody to detect the presence of Hashimoto autoimmune thyroiditis. Thyrothropin hormone levels should be monitored in patients with previously normal levels, bearing in mind thyroid cell reduction could occur slowly with unclear symptoms of hypothyroidism.[1,4,7] Imaging examinations such as ultrasound, thyroid scan, and CT-scan can only prove the presence of diffuse struma, and are thus unable to establish the etiologic diagnosis of Hashimoto autoimmune thyroiditis. Ultrasound findings of low echo should be in accordance with inflammation, and compared to ultrasound, thyroid scan may be better, since it could determine low uptake as that in hypothyroidism.

SUMMARY

Hashimoto autoimmune thyroiditis is a chronic autoimmune thyroiditis accompanied by diffuse enlargement of the thyroid gland (goitrous form). The autoimmune process is characterized by increased levels of antimicrosomal anti-thyroid antibodies (AMA) or antithyroglobulin antibody (anti-Tg). Clinical manifestations may take the form of euthyroidism, hypothyroidism, or even transient hyperthyroidism. Hypothyroidism is the most common thyroid dysfunction, even though only 10% is the classical hypothyroidism.

We hereby report 3 cases of Hashimoto autoimmune thyroiditis with different clinical manifestations, from the initial stage, the mild stage, and advanced stage. The first case demonstrated classical findings of Hashimoto autoimmune thyroiditis or the advanced stage. The sec-

ond case was initially in accordance with the initial stage, with normal levels of thyrothropin, but then increased to the mild case with increased thyrothropin levels. The third case is a case of remission after administration of thyroxin, with recurrence after 4 years. The three cases were treated with thyroxin in order to reduce complaints due to hypothyroidism as well as reduce the size of the thyroid gland enlargement with hypothyroidism.

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