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The clinical, laboratory and anatomical pathology profiles of Hashimoto's Thyroiditis patients at Dr. Soetomo General Academic Hospital Surabaya 2015 – 2020

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Abstract

The primary cause of hypothyroidism in the sufficient iodine area is Hashimoto's thyroiditis. Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis or chronic lymphocytic thyroiditis, is an autoimmune condition in which B cells and T cells slowly destroy the thyroid gland. To determine the diagnosis, we need the clinical, laboratory, cytological, and/or histopathology profiles. It aims to distinguish Hashimoto's thyroiditis from other diseases such as nontoxic goiter and Graves' disease. This retrospective descriptive study used data from the medical record of Dr. Soetomo General Hospital from 2015-2020. This study used total sampling and got 18 patients in total. The patients were mostly females (*n*=15), in the age group of 40-49 years old (*n*=8). The main complaint was an enlargement or nodule in the neck. The TSH (thyroid stimulating hormone) levels were majorly higher than the normal range (*n*=8) meanwhile the FT4 levels were mostly normal (*n*=6) and low (*n*=6). The positivity of TPOAb (antibody against thyroid peroxidase) is merely found in one patient. The majority of the result of the Doppler ultrasound examinations revealed Hashimoto's thyroiditis (*n*=7). FNAB (fine needle aspiration biopsy) was performed on 11 patients. A histopathology examination was also conducted on 9 patients who underwent thyroidectomy. All of the cytology and histopathology examinations confirmed Hashimoto's thyroiditis. Non-Hodgkin Lymphoma was found to coexist with 2 Hashimoto's thyroiditis cases. The findings were similar to the previous studies, except that among all the subjects, those who are 40-49 in age were primarily found in this study.

Keywords: Hashimoto's Thyroiditis; Autoimmune Thyroiditis; Clinical Profile; Laboratory Profile; Cytological Profile; Histopathological Profile

1. Introduction

Compared to other organs, autoimmune disease is known to often attack the thyroid gland [1]. Autoimmune thyroid disease is a complex and multifactorial disease in which an autoimmune response to thyroid antigens forms in individuals with a particular genetic background and exposure to certain environmental factors [2]. Hashimoto's thyroiditis and Graves' disease are well-known as autoimmune thyroid diseases. Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis or chronic lymphocytic thyroiditis, is an organ-specific autoimmune disorder characterized by autoimmune-mediated destruction of the gland [3]. To be specific, Hashimoto's thyroiditis is characterized by the occurrence of autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) with the slow development over years of subclinical and finally overt autoimmune hypothyroidism in some but not all patients [4]. The incidence of Hashimoto's thyroiditis has increased significantly in the last few decades [5,6]. The prevalence is higher in females than in males and escalates along with advancing age [7]. The incidence of Hashimoto's thyroiditis ranges from 3 - 6 cases per 10,000 population per year and the prevalence among females is at least 2% [8].

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To establish the diagnosis, we need the clinical, laboratory, cytology, and/or histopathology profile. It aims to distinguish Hashimoto's thyroiditis from other diseases such as nontoxic goiter and Graves' disease. The typical clinical finding in Hashimoto's thyroiditis is a symmetrical and diffuse enlargement of the thyroid gland [9]. Laboratory tests in the form of measuring the levels of FT4, TSH, and anti-TPO are required to help make this diagnosis. FT4 and TSH levels are requisite to assess thyroid function in Hashimoto's thyroiditis. Anti-TPO antibodies are the most important component of Hashimoto's thyroiditis (found in 90-95% of patients) while anti-thyroglobulin antibodies (TgAb) have a lower proportion than anti-TPO antibodies so they are not widely used for diagnosis [6]. FNAB (Fine Needle Aspiration Biopsy) is a procedure to obtain cytology specimens using a simple technique that is useful in the process of assisting discrete nodules in the thyroid gland [8]. Some patients also underwent thyroidectomy and histopathology examination. This study was carried out to describe the clinical, laboratory, and pathological profile of Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital in 2015 – 2020.

2. Material and methods

This study is a retrospective-descriptive study, with secondary data acquired from the electronic medical records of Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020. This study included 18 cases of Hashimoto's thyroiditis. The inclusion criteria was Hashimoto's thyroiditis patients diagnosed on fine-needle aspiration, histopathology examination, ultrasonography, thyroid function tests, and or anti-TPO antibodies. All Hashimoto's thyroiditis patients during the given period were the samples of this study which means that samples were collected using the total sampling technique. The data taken from the electronic medical records consist of their baseline data (age, gender, and main complaint), clinical examination, laboratory examinations (TSH levels, FT4 levels, TPOAb positivities, and thyroid Doppler ultrasound interpretation), cytology profile, and histopathology profile. Collected data were recorded for entry and processed using Microsoft Excel later on.

3. Results and discussion

Out of 18 Hashimoto's thyroiditis patients, majority (*n* = 15) were females and the remaining three were males (Table 1). Like other autoimmune diseases, Hashimoto's thyroiditis is also dominated by female patients [1]. The reasons autoimmune thyroid disease being more common in women are still not fully understood. The role of estrogen makes women more sensitive to autoimmune conditions due to the induction of a proinflammatory response [10].

Table 1 Distribution of demographic aspects for Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020

	Category	**N**	**%**
Gender	Female	15	83.3
	Male	3	16.7
Age group (years old)	<30	2	11.1
	30-39	5	27.8
	40-49	8	44.4
	50-59	2	11.1
	≥ 60 60	1	5.6

The majority of patients (*n* = 8) were in the age group of 40-49 followed by 5 patients in the age group of 30-39, 2 in less than 30, 2 in 50-59, and 1 patients in the age group of ≥ 60 (Table 1). This finding is different from the results of NHANES (National Health and Nutritional Examination Study) III with a US population of 17,353 subjects (1988-2004) which concluded that the prevalence of Hashimoto's thyroiditis increased with age group [11]. In that study, the prevalence increased five times (from 4.8% to 23.9%) between the second and ninth decades of life. Not much different from the results of the author's finding, the Robbins Basic Pathology textbook states that most Hashimoto's thyroiditis patients are 45-65 years in age [9].

Meanwhile, in another study in India, 107 cases of Hashimoto's thyroiditis were identified [12]. In that study, most patients (*n* = 68) were in the age group of 21-40, not in the eldest age group studied. The area where the study subjects

lived in India was not by a coastline which might still be an area of iodine deficiency. It indicated that the role of genetic susceptibility was more dominant in pathogenesis [12]. Another reason was the possibility of an earlier diagnosis [12]. Conversely, the trend which shows that the prevalence of Hashimoto's thyroiditis goes up along with age, suggesting that environmental injury plays a dominant role in the pathogenesis of the disease [7].

The main complaint of Hashimoto's thyroiditis patients when they came for the first time (table 2) was a lump/ enlargement/nodule in the neck in this study (100%). It was felt to be getting bigger in 5 patients (27.8%). A nodule in the neck that felt lumpy was complained of by two patients (11.1%), causing discomfort when swallowing in 1 patient (5.6%) and causing hoarseness in 1 patient (5.6%). On the other hand, complaints in terms of hyperthyroidism were palpitations (22.2%), trembling (16.7%), and excessive sweating (11.1%). Meanwhile, tingling in the hands and feet was reported as complaint that suggest hypothyroidism (5.6%).

The prevalence of goiters in Hashimoto's thyroiditis based on a rough estimation is around 5-10% [7]. The compressive effects of cervical structures that are anatomically adjacent to the thyroid manifest as dysphonia (includes hoarseness), dyspnea, and dysphagia, while systemic manifestations come from a loss of thyroid function and primary hypothyroidism [13]. The transient hyperthyroidism phase of Hashimoto's thyroiditis indicates the patient diagnosed during the early stage of the disease [14]. Complaints of patients with Hashimoto's thyroiditis are actually non-specific and resemble other clinical conditions [15].

Table 2 The main complaints for Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020

Main complaints	**N**	**%**
Lump on neck	18	100%
The lump feels bigger	5	27.8%
Heart pounding	4	22.2%
Shaking/tremors	3	16.7%
Discomfort when swallowing	1	5.6%
The nodule in the neck feels lumpy	2	11.1%
Hoarseness	1	5.6%
Neck feels stiff	2	11.1%
Tingling in hands and feet	1	5.6%
Easy/Frequent sweating	2	11.1%
Weight loss	2	11.1%
Out of breath	1	5.6%
Dyspnea	1	5.6%
Frequent bowel movements	1	5.6%

Based on information on the electronic medical record, physical examination results of the neck were available in 13 patients. A solid mass in the anterior neck region was found in 12 patients with tender consistency and moved when swallowing. The color was the same as the surrounding neck tissue. Dysphonia and dysphagia were discovered in 1 patient on physical examination.

Hashimoto's thyroiditis is marked by painless enlargement of the thyroid [8]. A lump seen without palpation is a form of Hashimoto's thyroiditis at a more advanced stage characterized by lymphocyte infiltration and high TSH stimulation. Hashimoto's thyroiditis is preceded by the enlargement of the neck that is still not visible to the naked eye and can only be confirmed by palpation or ultrasound investigation [16].

Laboratory examinations that greatly support the diagnosis of Hashimoto's thyroiditis were the positivity of TPOAb and thyroid function test, especially FT4 and TSH levels. Table 3 summarizes the laboratory profile of the patients. The reference range of TSH levels for patients over 18 years old at Dr. Soetomo General Hospital is 0.55 – 4.78 μIU/mL. The patient's lowest and highest TSH levels were 0.005 μIU/mL and 39.761 μIU/mL, respectively. Most patients (44.4%) had TSH levels higher than the upper limit (> 4.78 μIU/mL). The number of patients with TSH levels less than the lower limit (< 0.55 μIU/mL) was the same as the number of patients with normal TSH levels (0.55 – 4.78 μIU/mL) which was 27.8% (*n* = 5).

The reference FT4 levels at Dr. Soetomo General Hospital are 0.89 – 1.76 pg/mL. The data were available in 15 patients out of a total of 18 Hashimoto's thyroiditis patients. The patient's lowest and highest FT4 levels were 0.35 pg/mL and 4.61 pg/mL respectively. The number of patients with FT4 levels less than the lower limit (0.89 pg/mL) was the same as the number with normal FT4 levels (0.89 – 1.76 pg/mL), namely six patients each (33.3% of the total number of patients or 40 % of the 15 patients who had data on FT4 levels). FT4 levels were more than 1.76 pg/mL in 16.7% of patients (*n* = 3).

Hashimoto's thyroiditis may occur with hypothyroidism, euthyroidism, and hyperthyroidism [7]. This is understandable because of the natural history of Hashimoto's thyroiditis, namely the gradual loss of thyroid function [17]. Hashimoto's thyroiditis patients with hypothyroidism at the time of diagnosis are likely to be at the late phase of the disease. Some patients experience hyperthyroidism due to a temporary hyperthyroid phase known as hashitoxicosis [12]. Hashimoto's thyroiditis is characterized by an initial phase of transient hyperthyroidism followed by a chronic phase of subclinical or overt hypothyroidism [14].

TPOAb level data was available in one of the eighteen patients who were involved in this study, namely 118.72 U/mL with a positive anti-TPO antibody interpretation because it exceeded the reference level (> 5.61 U/mL). The positivity of TPOAb was unknown in the other 17 patients' electronic medical records.

A positive result for serum TPOAb confirms the diagnosis of Hashimoto's thyroiditis [7]. However, about 10% of Hashimoto's thyroiditis patients are negative on serum TPOAb because antibodies are only produced in the thyroid gland in some cases [18,19]

Table 3 The TSH levels, FT4 levels, and TPOAb positivity of Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020

	Category	**N**	**%**
TSH levels (μIU/mL)	< 0.55	5	27.8
	0.55 – 4.78	5	27.8
	>4.78	8	44.4
FT4 levels (pg/mL)	< 0.89	2	11.1
	0.89 – 1.76	5	27.8
	>1.76	8	44.4
	N/A	2	11.1
TPOAb	Positive	1	5.6
	N/A	17	94.4

Thyroid Doppler ultrasound interpretations were available in 16 patients. The conclusion of the examination (Table 4) supported the features of Hashimoto's thyroiditis in 7 patients with characteristic enlargement of the lobe or isthmus with decreased parenchymal echo intensity (hypoechoic) and heterogeneous echotexture. Other interpretations were malignancy-suspected (*n* = 2), diffuse goiter (*n* = 3), bilateral multinodular goiter (*n* = 3), and single thyroid nodule (*n* = 1).

Typical sonographic signs of Hashimoto's thyroiditis are patchy echo patterns or hypoechogenicity, both heterogeneous and diffuse, which are significant [20]. Hypoechogenicity depicts lymphocyte aggregation [16]. The sensitivity of thyroid

ultrasonography is reported to be high because the ultrasound pattern, either in the form of a hypoechoic or irregular pattern, can be identified before the serum TPOAb are proven to be positive [16,21]. In a study with a sample of 89 Hashimoto's thyroiditis patients and 40 healthy controls, it was ascertained that hypoechogenicity in Hashimoto's thyroiditis patients was associated with hypothyroidism [22]. Apart from the typical features of Hashimoto's thyroiditis, some patients in this research had diffuse enlargement whereas some others presented bilateral multinodular goiter. Nodular goiter is thought to form in the early stages of the disease course while diffuse enlargement is found at an advanced stage where hormonal and clinical changes appear more clearly [14].

Table 4 Thyroid Doppler ultrasound interpretations of Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020

Interpretations	N
Support the description of Hashimoto's thyroiditis	7
Malignancy-suspected	2
Diffuse goiter	3
Single nodule	1
Bilateral multinodular goiter	3
No data	2

Eleven patients went through an FNAB examination to support the diagnosis. Evaluation of the specimens from 11 patients (100%) yielded the same conclusion, which is by the microscopic appearance of Hashimoto's thyroiditis. It can also be called chronic lymphocytic thyroiditis. A total of 2 patients who had undergone FNAB also received further thyroidectomy then followed a histopathological evaluation of the collected tissue afterwards.

After 2 punctures per nodule, smears were made for microscopic examination. The smears of 11 patients who underwent FNAB showed microscopic features in the form of groups of normal follicular epithelial cells (n = 10), scattered lymphocyte cells revealed in all preparations (n = 11), Hürthle/oxyphilic cells (n = 2), histiocytes/giant cells (n = 3), and fire flare (n = 1). These findings are summarized in table 5.

Table 5 Cytomorphological profile of Hashimoto's thyroiditis patients at Dr. Soetomo General Hospital, Surabaya in 2015-2020

Cytological Feature	N
Groups of normal follicular epithelial cells	10
Infiltration of lymphocyte cell	11
Hürthle/oxyphilic cells	2
Histiocytes/giant cells	3
Fire flare	1

Cytological signs/hallmarks of Hashimoto's thyroiditis precede the emergence of a clinical diagnosis (Staii, 2010). As priorly explained, the diagnosis of Hashimoto's thyroiditis is established in the presence of TPOAb. However, patients with Hashimoto's thyroiditis who experience hypothyroidism are more often positive for TPOAb than patients with Hashimoto's thyroiditis whose thyroid function is still normal/euthyroid [23]. The description of lymphocyte infiltration in the thyroid gland represents the main feature of Hashimoto's thyroiditis [24]. In this study, these features were found in all patients who underwent FNAB examination. Lymphocyte infiltration (especially T cells) indicates that the thyroid gland is gradually replaced by fibrosis or thyrocyte atrophy [24].

Hürthle cells are another characteristic feature along with lymphocytic infiltration. Meanwhile, histiocytes and giant cells are found in some cases but are not of diagnostic value [12]. Fire flares can be found in a variety of benign and

malignant thyroid lesions [12]. The appearance of fire flares is significantly associated with hyperthyroidism thus, indicating hyperfunction of follicular thyroid cells [25].

Thyroidectomy was done in 9 patients in total followed by histopathological examinations. Previously, two of them had had FNAB. The most common conclusion from the evaluation of anatomical pathology in 9 patients who underwent thyroidectomy was Hashimoto's thyroiditis (*n* = 6). Other conclusions were Non-Hodgkin Lymphoma that coexists with Hashimoto Thyroiditis (*n* = 2) and Hashimoto's thyroiditis with adenomatous goiter (*n* = 1).

Table 6 Conclusion of Pathological Examination after Thyroidectomy

Conclusion	**N**
Non Hodgkin Lymphoma coexisting with Hashimoto Thyroiditis	2
Hashimoto’s thyroiditis coexisting with adenomatous goiter	1
Hashimoto’s thyroiditis	6

Macroscopically, the thyroid tissue was identified for its size, weight, and characteristics. The smallest thyroid tissue size was 3.5 x 2.5 x 2 cm, meanwhile the largest was 19 x 15 x 9 cm. There were six thyroidectomy patients whose thyroid tissue weight was known, the lightest was 7.8 grams, while the heaviest was 900 grams. The consistency of dense, spongy tissue with the characteristics of the outer surface is smooth, partly rough, and white and gray in color.

The most common conclusion from the evaluation of anatomical pathology in 9 patients who underwent thyroidectomy was Hashimoto's thyroiditis (n = 6), featuring groups of normal follicular epithelial cells (cuboidal cells with rounded oval nuclei, smooth chromatin, sufficient cytoplasm), lymphocyte infiltration, some forming lymphollicular tissue with a germinal center, and Hürthle/oxyphilic cells. Regarding with the lymphocytic infiltration of the thyroid, there were six patients with a microscopic description of lymphoid follicle tissue with a germinal center appearance. The rest had a microscopic appearance of a diffuse infiltration of lymphocytic inflammatory cells forming a lymphoid follicle appearance. The nine patients were concluded as Hashimoto's thyroiditis on anatomical pathology evaluation.

Hakaru Hashimoto was the first to describe a disease called “lymphomatous goiter” (currently known as Hashimoto's thyroiditis) in four patients with chronic thyroid disorders who had anatomic pathological features of diffuse lymphocytic infiltration with germinal centers, fibrosis, parenchymal atrophy, and eosinophilic changes in some follicular cells. He emphasized the lymphoid infiltration and lymphoid follicle formation with germinal centers. This is related to the gradual failure of the thyroid caused by progressive destruction of thyrocytes due to cytotoxic T-cell infiltration, local circulation of cytokines, and antibody-dependent cytotoxicity [9,24].

Non-Hodgkin Lymphoma coexisting with Hashimoto Thyroiditis was confirmed in 2 patient. The patients underwent a Doppler ultrasound, an FNAB, and four pathological examinations to affirm the diagnosis. On ultrasound, multiple heteroechoic masses were found. FNAB suggested Hashimoto's thyroiditis. Macroscopically, the thyroid preparation appeared in the form of multilobulated tissue. Furthermore, the incisional biopsy examination exhibited groups of diffuse lymphoid cells, the proliferation of oval nucleated cells, mild pleiomorphic, hyperchromatic, thin cytoplasm, and mitotic 6/10 HPF so that non-Hodgkin lymphoma was suspected. Examination continued with neck IHC (immune-histo-chemistry examination) with the conclusion of low-grade non-Hodgkin lymphoma. Subsequently, one piece received tissue showed diffuse thyroid tumor growth consisting of proliferating anaplastic cells and in another area thyroid tissue with follicles lined with a single layer of rounded cuboidal epithelium, extensive eosinophilic cytoplasm with infiltration of lymphoid cells. Furthermore, a neck IHC examination was carried out with the conclusion of Non-Hodgkin Lymphoma coexisting with Hashimoto Thyroiditis, B cell type, and high grade.

Conclusion Non-Hodgkin Lymphoma in the right lobe and Hashimoto's thyroiditis in the left lobe were found in 1 patient. Macroscopically, a solid nodule 2.3 x 2 x 1.7 cm was seen on the slide. Microscopic examination of the right lobe showed a thyroid section with diffusely arranged tumor growth consisting of anaplastic cell proliferation, rounded nuclei, relatively monotonous, coarse chromatin, prominent nucleoli, narrow cytoplasm, mitotic 27/10 HPF, and invasive tumor growing between the stroma to the edge of surgical resection. While the isthmus and left lobe showed the proliferation of follicles of various sizes, the lumen was filled with colloidal material covered with a single layer of normal follicular epithelium, including lymphoid of various sizes with a reactive germinal center and mature lymphoid cells.

Table 7 Histopathology Features of Thyroid Tissues after Thyroidectomy

Histopathology feature	**N**
Group of normal follicular epithelial cells	9
Infiltration of lymphocytes	9
lymphoid follicle formation with germinal center	6
Hürthle/oxyphilic cell	4

As early as 1893, Rudolf Virchow proposed a link between chronic inflammation and cancer formation. This hypothesis has been lasting over the centuries. With this understanding, it has been postulated that Hashimoto's thyroiditis as chronic inflammatory thyroid disease is also associated with an increased risk of suffering from thyroid cancer [7]. Inflammation of the thyroid epithelium can trigger remodeling of the tissue so that there may be a greater chance of mutation to occur if the cells continue to divide [23]. It is known that Hashimoto's thyroiditis with solitary and multinodular nodules is at risk for thyroid malignancy [9,26].

Regarding the diagnosis of Hashimoto's thyroiditis with adenomatous goiter, this is in line with the fact that iodine supplementation universally increases the incidence of autoimmune thyroid in patients with previous colloid/adenomatous goiter [25]. This phenomenon explicates the dual features of Hashimoto's thyroiditis with colloid/adenomatous goiter.

4. Conclusion

Hashimoto's thyroiditis patients were mostly females in the age group of 40-49. The main complaint was an enlargement or nodule in the neck. The TSH levels were majorly higher than the normal range meanwhile the FT4 levels were mostly normal and low. They indicated the subclinical and overt hypothyroidism. The majority of the result of the Doppler ultrasound examinations depicted Hashimoto's thyroiditis. Although the data of TPOAb positivity was merely found in one patient. All of the cytology and histopathology examinations confirmed Hashimoto's thyroiditis. Non-Hodgkin Lymphoma and adenomatous goiter were found to coexist with 2 and 1 Hashimoto's thyroiditis cases respectively.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors report no conflict of interest.

Statement of ethical approval

This study was approved by the health research ethic committee of Dr. Soetomo General Academic Hospital Surabaya (No. 0619/LOE/301.4.2/IX/2021) on September 28th 2021.

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