



Hashimoto's Thyroiditis from the General Surgeon's Perspective

Genel Cerrah Bakışından Hashimoto Tiroiditi

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Dear Readers,

In this issue, I will talk about a general surgeon's perspective and approach to Hashimoto's thyroiditis (HT).

HT is one of the most common autoimmune diseases characterized by thyroid-specific autoantibodies. Although its etiology has not been fully elucidated, genetic elements, environmental factors and epigenetic effects are considered among the causes (1). The prevalence of HT varies between 5.8% and 14.2% depending on geographical locations (2). Cellular and humoral immunity play a key role in the development of the disease; therefore, inflammatory infiltration of T and B cells is often found. Histopathological features of the disease include lymphoplasmacytic infiltration, germinal-centered lymphoid follicle formation, and parenchymal atrophy. Additionally, the appearance of large follicular cells and oxyphilic cells or Askanazy cells is often associated with HT. Clinically, HT is characterized by systemic symptoms due to damage to the thyroid gland, and hypothyroidism often develops. The diagnosis of HT is mostly made clinically. Positivity of serum antibodies against thyroid antigens such as thyroid peroxidase (TPO) and thyroglobulin and lymphocytic infiltration in cytological examination are helpful parameters in diagnosis. The main principle of treatment is based on the treatment of hypothyroidism. The relationship between HT and a possible malignant transformation has been suggested in many studies and immunological/hormonal pathogenic effects are thought to be involved, but the specific correlation is still debated and needs to be further investigated in prospective studies (3).

In patients with HT, thyroid antibodies are formed through various immune processes. These antibodies attack thyroid tissues and fibrosis occurs, resulting in loss of thyroid function. Hypothyroidism develops due to this insult. Clinically, symptoms such as weight gain, constipation, increased sensitivity to cold, and dry skin occur. HT can cause cardiovascular diseases such as coronary heart disease. Additionally, HT is a risk factor for the development of thyroid cancer.

The prevalence of HT is increasing nowadays. It is known that genetic predisposition, environmental factors, immune system, cytokines and vitamin D deficiency play an important role in the pathogenesis of HT (4).

Factors Involved in Etiology and Pathogenesis

Genetic predisposition plays an important role in the pathogenesis of HT. Many studies have reported that there is a genetic predisposition to HT. For example, while the prevalence of HT is higher in Latin America, it is lower in Africa and Asians (5). Based on a Swedish twin study in which the HT concordance was shown to be 0.29 and 0.1 for monozygotic and dizygotic twins, respectively, and the heritability was 0.64, and the higher concordance rate for monozygotic twins than dizygotic twins confirmed that such disease sharing was dependent on common genes (5,6). Recombinant interleukin-2 receptor alpha, human leukocyte antigen (HLA), protein tyrosine phosphatase non-receptor type 22, and cytotoxic T lymphocyte-associated antigen-4 are susceptible sites for HT. These loci have the potential to

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disrupt T cell regulation and peripheral immune tolerance and play an important role in the pathogenesis of HT (7).

Environmental factors have an impact on the pathogenesis of HT. In autoimmune reactive diseases, an environment devoid of microbial agents and hygiene have been shown to have a strong relationship with the incidence of autoimmune diseases. One study suggested that women born in the summer months had a 2% higher incidence of HT compared to the general female population (8). Prolonged exposure to stressful situations may increase the incidence of HT. Meat, in particular, is an important nutritional factor that has been shown to increase the risk of thyroid autoimmunity, however, plant and fat-free foods containing fiber and antioxidants have been shown to reduce the risk of HT (4).

It is known that trace elements play an important role in the emergence of the disease. Iodine plays an important role, especially in thyroid diseases. Thyroid epithelial cells take up the iodine found in the blood and iodine tyrosine molecules by catalyzing it with hydrogen peroxide. The iodinated products are then converted into T3 and T4 by TPO (9). Studies have shown that increased iodine intake increases the risk of AITD. Both salt iodization programs and excessive supplementation can cause hypertension (10). The mechanisms currently discussed are: 1- increase the immunogenicity of thyroglobulin; 2- activate the autoimmune response and triggers signaling pathways that lead to apoptosis, which causes the destruction of thyroid tissue; 3- cause increased oxidative stress; 4- impair peripheral tolerance due to inhibition of regulatory T cells (Tregs) (9,11). Selenium is an essential micronutrient that plays an important role in immune-related diseases. The thyroid gland is the largest reserve of selenium in the body. SELENOS is a susceptibility gene for HT which is expressed in thyroid follicular cells. It encodes the family of selenoproteins which are involved in cellular stress and immune inflammatory responses. Selenium supplementation has an immune stimulating effect and can inhibit HLA-DR expression in thyroid cells, reduce thyroid autoimmunity, and this is evidenced by increased T and innate immune cell function. Therefore, selenium deficiency also plays a role in the pathogenesis of HT (12,13). Iron plays an important role in hemoglobin and myoglobin and is involved in many important metabolic processes. TPO can only be activated after binding to repaired "Hem I" and participates in thyroid hormone synthesis, therefore iron content affects T3-T4 synthesis. The thyroid-small intestine axis is closely related to HT. Hypothyroidism can cause digestive disorders, impaired bowel function, and decreased iron absorption. Iron deficiency affects the regulation of thyroglobulin with iodine, and combining of iotyrosine molecules, which causes a decrease in T3 and T4 production, causing hypothyroidism (9). HT is often associated with autoimmune gastritis, with large amounts of anti-parietal cell antibodies found in the serum. As the disease progresses, this evolves into severe atrophic gastritis and reduced gastric acid secretion, resulting in the body's inability to effectively absorb iron from food, resulting in iron malabsorption. Zinc is a trace element closely related to thyroid metabolism. It

promotes the synthesis of hypothalamic thyrotropin-releasing hormone and thyroid-stimulating hormone (TSH), and is also a structural component of the T3 receptor. It also functions as a thyroid hormone-binding transcription factor that regulates the expression of thyroid hormones by regulating thyroid hormone deficiency. Dietary zinc deficiency and low serum zinc concentration can lead to changes in thyroid hormone metabolism and even thyroid structure. Zinc deficiency reduces free T3-T4 levels in serum. In addition, zinc and thyroid function may affect each other; zinc deficiency causes decreased thyroid function, and thyroid insufficiency leads to inadequate zinc absorption (14,15).

Vitamin D deficiency is one of the causes of HT. In this case, the greater the vitamin D deficiency, the higher the possibility of HT (16). Vitamin D concentration is positively associated with the cytokines TNF- α , IL-5, and IL-17, which regulate the cellular immune response against inflammation in patients with HT and are secreted from Th1 cells (17). Since cellular immunity is the main element of pathogenesis in patients with HT, the relationship between vitamin D and these cytokines suggests that vitamin D is involved in the pathogenesis of HT. Dysbiosis in the intestinal flora contributes to HT triggers.

Immunological factors are among the main factors that play a role in HT. As is known, HT is an autoimmune disease characterized by thyroid-specific autoantibodies. Inflammatory infiltration of T and B cells constitutes the main pathogenesis (5). In the context of genetic predisposition and environmental factors, errors in innate immune function produce antibodies against thyroid antigens, causing cytotoxic damage to thyroid cells and immune dysfunction. This causes cellular and humoral immune responses and destruction of thyroid epithelial cells, leading to disease. Cellular immunity; some autoreactive T cells escape immune regulatory control and enter peripheral tissues, leading to autoimmune disease. Activation of T cells stimulated by peripheral antigens, co-stimulatory factors or specific cytokines leads to the formation of different T cell subpopulations (18). T helper cells and Tregs are important T cells involved in the autoimmune response (19). Tregs and Th cells are key regulators of inflammation and play an important role in immune tolerance. CD4 is the main marker on the Th surface, and Th1, Th2, Th17, and follicular helper T cell subtypes are closely associated with the development of HT.

The Relationship between Autoimmune Thyroiditis and Cancer

Hashimoto's thyroiditis is also autoimmune aseptic inflammation. Research shows that chronic inflammation is a very important factor in the development of cancer (20). Therefore, more research institutes are investigating the relationship between HT and cancer. However, as research increases, debates and different opinions continue to emerge about whether HT is related to cancer development. In the meta-analysis study conducted by Hu et al. (2) in 2022, 12,917 patients and 60,509 control subjects in 11 case-control studies and 12 cohort studies were included. In the study conducted on patients with HT, 13

types of human cancer were examined: thyroid cancer, breast cancer, lung cancer, stomach cancer, liver cancer, colorectal cancer, uterine cancer, cervical cancer, ovarian cancer, prostate cancer, bladder cancer, kidney cancer and hematological cancers. Relative risk/probability ratios of cancer types in patients with HT were reported. The result of meta-analysis showed that the rate of thyroid cancer was highest in patients with HT. The rate of thyroid cancer in patients with HT in 21 studies ranged from 0.61% to 58.43%, with a mean rate of 25.01%. The mean rate of breast cancer 1.40% (0.99%, 1.82%), respiratory organs cancer 1.06% (0, 2.15%), genitourinary cancer was 1.2% (0.3%, 2.1%), digestive organs cancer 2.21% (0.46%, 3.95%), and leukemia 0.37% (0.13%, 0.61%). Only one document mentioned malignant lymphoma, and 2 patients were found among 2,036 patients with HT. Among 329 patients with HT, 3 patients of myeloma were found and no case was found in the control group (2).

There is no doubt about the relationship between AIT (autoimmune thyroiditis) and papillary thyroid carcinoma (PTC). Fiore et al. (21) analyzed the rate of PTC, high TSH levels and the presence of antithyroid antibody (ATA) in 13,738 patients with autoimmune thyroid disease (AITD) [3,914 on l-thyroxine (L-T4) treatment and 9,824 on no treatment]. The prevalence of PTC was found to be higher in patients with nodular-AIT than in those with nodular goiter. An increase in TSH levels has also been observed in patients with PTC. Both TSH level and PTC incidence were lower in patients receiving LT-4 treatment. Similar findings have been observed in other studies (21). Thyroid autoimmunity and high TSH levels are considered independent risk factors for thyroid cancer in different articles. A high prevalence of PTC was found in patients with chronic hepatitis C and mesothelioma, especially in the presence of autoimmune thyroiditis (22). Of patients with both PTC and AITD, 5-10% may develop aggressive disease and require systemic therapy.

Diagnosis of Hashimoto's Thyroiditis

Diagnosis of HT is based on clinical symptoms, ATA and histological features. Serum anti-TPO antibodies are considered the hallmark of HT and are present in approximately 95% of patients. Instead, anti-thyroglobulin antibodies are found in a lower percentage of patients (60-80%) and are therefore less reliable for diagnosis. It appears that anti-thyroglobulin antibodies may be an expression of an initial immune response, whereas anti-TPO antibodies may be a result of a later immune response. Clinical features include both local and systemic manifestations, as well as features specific to individual forms of HT. Local symptoms result from compression of cervical structures anatomically close to the thyroid gland and include dysphonia, dyspnea, and dysphagia. Systemic findings result from loss of function of the thyroid gland and subsequent primary hypothyroidism. Given the profound and broad influence of thyroid hormones on most organs and tissues, the signs and symptoms of hypothyroidism are numerous and variable.

The diagnosis of HT is currently made by a combination of clinical features, the presence of serum antibodies against thyroid antigens (mainly thyroperoxidase and thyroglobulin), and the appearance on a thyroid sonogram. Radioactive iodine uptake of the thyroid gland and cytological examination of thyroid aspirate are used less frequently.

Cytological examination is not routinely performed, but only when a thyroid nodule with suspicion of malignant transformation is found. Additionally, ultrasonographic features of HT may make nodule identification and aspiration difficult. Finding lymphocytes in contact with thyroid cells is considered the most important element in making the differential diagnosis between HT and thyroid tumors (23).

Radiological evaluation of HT is usually made with ultrasonographic examination. Neck ultrasound has become the most commonly used imaging tool in patients with thyroid diseases. It shows characteristically decreased echogenicity in HT. The normal thyroid gland, composed of thyroid follicles of various sizes making the lobes appear bright. In HT, on the contrary, thyroid follicles are destroyed and replaced by small aggregates of lymphocytes, so that the echogenicity of the thyroid parenchyma decreases markedly and becomes similar to that of the surrounding muscles. Various forms of HT have unique characteristics. For example, hypoechogenicity is more prominent in the IgG4-related variant, and in the fibrous variant it is accompanied by disorganization and nodularity, given the conspicuous accumulation of collagen fibers. Thyroid ultrasound can also measure the volume of the thyroid gland. Thyroid ultrasound can also be combined with Doppler or elastography. In addition, ultrasound is used to guide needle placement during fine needle aspiration into the thyroid nodule (24).

Thyroid Function Tests, Radioiodine Uptake and Fine Needle Aspiration

Evaluation of thyroid functions in patients with HT is performed by measuring serum thyrotropin (TSH) and free thyroxine (FT4) levels. TSH is the most important index for monitoring thyroid functions because its level fully adapts to even minimal changes in circulating thyroid hormones. Because results are variable, 24-hour thyroid radioactive iodine uptake is now rarely used to diagnose HT. However, it is beneficial in painless thyroiditis. During the hyperthyroid phase of this variant of HT, radioiodine uptake actually decreases (<5%) rather than increases. This is because the increase in circulating thyroid hormones is not due to increased function of the thyroid gland (hyperthyroidism), but rather to the destruction of thyroid follicles and the release of previously formed thyroid hormones (thyrotoxicosis).

When the patient has a thyroid nodule, fine needle aspiration is performed. Most thyroid nodules are true nodules and the majority are benign tumors. However, in the fibrous variant of HT, "pseudo-nodules" may be present, given that dense keloid-like fibrosis distorts the thyroid structure and gives the gland a lobular appearance. When thyroid antibodies and a nodule are present, it is difficult to determine whether the patient has two

concomitant thyroid diseases or just the fibrous variant of HT. Therefore, fine needle aspiration is performed and cytological results may be difficult to interpret. In HT, cytologic examination shows a polymorphic population of lymphoid cells (small mature lymphocytes, larger activated lymphocytes, and occasionally plasma cells) accompanied by Hurthle cells. Lymphocytes are often in contact with thyroid cell groups, and this feature is thought to be useful in distinguishing HT from thyroid neoplasms (25). However, some aspirates lack lymphoid cells and consist almost entirely of Hurthle cells, making it difficult to determine whether these are Hurthle cells found in HT or those found in other oncocyctic lesions of the thyroid, such as oncocyctic adenomatoid nodule.

Treatment of Hashimoto's Thyroiditis

Hashimoto's thyroiditis is essentially a medical disease. Its treatment is similar to the treatment of patients with goiter. The American Thyroid Association has guidelines for the management of thyroid disorders. It has been stated that medical options for goiter treatment primarily consist of iodine replacement, thyroid hormone replacement, thyroid hormone suppressive therapy and radioactive iodine (26).

The use of thyroid hormone (levothyroxine) in patients with iodine deficiency can cause the goiter to shrink by 15% to 40% in approximately 3 months. However, available literature indicates that goiter can be expected to return to its pretreatment size after discontinuation of thyroid hormone supplementation.

Levothyroxine replacement can be used and is routinely recommended to normalize high TSH levels due to hypothyroidism, which may be associated with a reduction in goiter size. In contrast, levothyroxine can also be used to suppress the serum TSH level below the lower limit of the normal range. This causes normal thyroid tissue to invert to a much greater extent than pathological thyroid tissue; therefore, its effectiveness in large goiters is limited and suppressive therapy is not routinely recommended. On the other hand, lifelong suppression is required, and such long-term TSH suppression therapy is associated with an increased risk of adverse side effects such as atrial fibrillation and osteoporosis, especially in postmenopausal women.

Radioactive iodine therapy is widely used to reduce goiter size in patients with non-toxic multinodular goiter. Patients who are considered risky surgical candidates and have goiters with compressive symptoms that range in size from medium to large may be suitable candidates for radioactive iodine. Radioactive iodine ablation has been associated with a reduction in goiter volume, but most of the reduction occurs in the first few months of treatment. However, there are complications associated with the treatment; (i) regrowth of goiter after treatment (15-25% potential increase in size) and narrowing of the trachea, (ii) transient thyrotoxicosis resulting from radiation thyroiditis; (iii) the subsequent development of subclinical or overt hypothyroidism; and (iv) the occurrence of secondary hyperthyroidism/Graves disease and radiation-induced malignancies (such as breast cancer), which have been reported

in patients receiving radioactive iodine for ablation of euthyroid goiter.

Surgery

Surgery is rarely indicated for thyroiditis. Unlike medical treatment, which provides at best a partial reduction in goiter volume, surgery offers definitive treatment by removing the goiter, although it carries the risk of laryngeal nerve damage, hypoparathyroidism, bleeding or hematoma.

There are also publications advocating that surgical treatment for HT is contraindicated, except when the disease is associated with nodular lesions suggestive of malignancy (27).

The most basic surgical indication in HT is the presence of a nodule and the presence or suspicion of malignancy as a result of FNAB. Surgery may be performed in patients who do not show improvement in compressive symptoms despite long-term treatment with L-T₄ and no decrease in goiter size, patients with shortness of breath and difficulty swallowing due to compression on the trachea or esophagus, growth of the nodule, localized progressive pain, for prevention of complications arising from extension to the mediastinum, or sometimes for cosmetic reasons.

The prevalence of thyroid cancer in patients with HT varies from 0.4% to 28% in different surgical series. However, there are studies arguing that the risk does not increase. A meta-analysis study has also been published concluding that HT is associated with all thyroid malignancies except follicular and anaplastic thyroid cancer. The risk of lymphoma in patients with HT is known. Although there are different opinions about the risk of cancer coexisting with thyroiditis, the surgeon treating thyroiditis should keep this risk in mind when determining the indication (27,28).

The recommended method of surgery is total thyroidectomy. If there is a risk of adhesion and injury to the recurrent laryngeal nerve (RLN), near total thyroidectomy can be performed.

Thyroidectomy is technically more difficult in patients with thyroiditis than patients without thyroiditis, because of requiring more operating time and longer hospital stay. Although some studies indicate no difference, most studies have found a higher risk of temporary or permanent hypocalcemia and/or RLN palsy. Surgery in patients with thyroiditis should be performed by a senior, specialist surgeon who is experienced in difficult thyroidectomies and can manage intraoperative difficulties such as bleeding and identification of the RLN and/or parathyroid gland. This will reduce post-operative complications.

Complications of surgery for HT are similar to complications experienced in other thyroid surgeries. These include bleeding, RNL injury, hoarseness, inability to raise the voice, and temporary or permanent hypoparathyroidism. Wound infection is rare. Intraoperative bleeding may be directly related to venous congestion. Rarely, pneumothorax may occur.

Postoperative calcium levels should be taken into consideration. Measurement of parathyroid hormone level in the postoperative period and, if necessary, the need for calcium supplements with

calcitriol should be determined before the patient is discharged. It is also important to start the patient on levothyroxine treatment after the surgery. The usual dose is 1.4-1.6 µg/kg per day (based on actual body weight), testing of TSH level should be planned 4-6 weeks after surgery and titration of dose should be performed as necessary. Patient education at discharge should include signs/symptoms of hypocalcemia, hematoma, infection, or airway distress (29,30).

Last Words

To date, much progress has been made in the knowledge and treatment of HT. However, the mechanisms that lead to impaired tolerance of the immune system and the resulting autoimmune response against the thyroid gland and the onset of the disease are still controversial.

Although many genetic and environmental factors that can trigger an autoimmune response have been identified, the exact etiopathogenesis of HT is still unknown. Studies showing that excess iodine due to iodine added to foods in order to prevent iodine deficiency increases the formation of HT, and the warnings of the World Health Organization in this regard should be taken into consideration. The importance of epigenetic factors has been emphasized recently, but more studies are needed to fully understand their roles. Treatment of HT, currently focusing on the clinical symptoms of the disease, should in the future address the autoimmune mechanism that causes the destruction of the thyroid parenchyma and the resulting hypothyroidism. A better understanding of epigenetic modifications and autoimmune pathogenic mechanisms will contribute to a more accurate diagnosis of HT, a more adequate choice of treatment approach, and a more accurate prediction of treatment outcomes.

References

- Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, et al. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmun Rev* 2020;19:102649.
- Hu X, Wang X, Liang Y, Chen X, Zhou S, Fei W, et al. Cancer Risk in Hashimoto's Thyroiditis: a Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2022;13:937871.
- Cayres LCF, de Salis LVV, Rodrigues GSP, Lengert AVH, Biondi APC, Sargentini LDB, et al. Detection of Alterations in the Gut Microbiota and Intestinal Permeability in Patients With Hashimoto Thyroiditis. *Front Immunol* 2021;12:579140.
- Jin B, Wang S, Fan Z. Pathogenesis Markers of Hashimoto's Disease-A Mini Review. *Front Biosci (Landmark Ed)* 2022;27:297.
- Ajjan RA, Weetman AP. The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. *Horm Metab Res* 2015;47:702-10.
- Weetman AP. An update on the pathogenesis of Hashimoto's thyroiditis. *J Endocrinol Invest* 2021;44:883-90.
- Hwangbo Y, Park YJ. Genome-Wide Association Studies of Autoimmune Thyroid Diseases, Thyroid Function, and Thyroid Cancer. *Endocrinol Metab (Seoul)* 2018;33:175-84.
- Thvilum M, Brandt F, Brix TH, Hegedüs L. Month of birth is associated with the subsequent diagnosis of autoimmune hypothyroidism. A nationwide Danish register-based study. *Clin Endocrinol (Oxf)* 2017;87:832-7.
- Hu S, Rayman MP. Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. *Thyroid* 2017;27:597-610.
- Luo Y, Kawashima A, Ishido Y, Yoshihara A, Oda K, Hiroi N, et al. Iodine excess as an environmental risk factor for autoimmune thyroid disease. *Int J Mol Sci* 2014;15:12895-912.
- Kolypetri P, King J, Larijani M, Carayanniotis G. Genes and environment as predisposing factors in autoimmunity: acceleration of spontaneous thyroiditis by dietary iodide in NOD.H2(h4) mice. *Int Rev Immunol* 2015;34:542-56.
- Avery JC, Hoffmann PR. Selenium, Selenoproteins, and Immunity. *Nutrients* 2018;10:1203.
- Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, et al. Hashimoto's thyroiditis: Epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab* 2019;33:101367.
- Beserra JB, Morais JBS, Severo JS, Cruz KJC, de Oliveira ARS, Henriques GS, et al. Relation Between Zinc and Thyroid Hormones in Humans: a Systematic Review. *Biol Trace Elem Res* 2021;199:4092-100.
- Aziz MA, Habil NY, Diab AKS. Effectiveness of zinc supplementation in regulating serum hormonal and inflammatory status in hypothyroidism patients. *Medical Journal of Babylon* 2016;13:347-53.
- Salem TM, Abdelmonem E, Fayad A. Hashimoto's thyroiditis, iron, and vitamin D deficiency among Egyptian female patients: associations and possible causalities. *Hormones (Athens)* 2021;20:833-6.
- Botelho IMB, Moura Neto A, Silva CA, Tambascia MA, Alegre SM, Zantut-Wittmann DE. Vitamin D in Hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status. *Endocr J* 2018;65:1029-37.
- Ramos-Levi AM, Marazuela M. Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms. *Endocrinol Nutr* 2016;63:421-9.
- Sekiya T, Kagawa S, Masaki K, Fukunaga K, Yoshimura A, Takaki S. Regulation of peripheral Th/Treg differentiation and suppression of airway inflammation by Nr4a transcription factors. *iScience* 2021;24:102166.
- Malhab LJB, Saber-Ayad MM, Al-Hakm R, Nair VA, Paliogiannis P, Pintus G, et al. Chronic Inflammation and Cancer: The Role of Endothelial Dysfunction and Vascular Inflammation. *Curr Pharm Des* 2021;27:2156-69.
- Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A, et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. *Endocr Relat Cancer* 2011;18:429-37.
- Ferri C, Sebastiani M, Giuggioli D, Colaci M, Fallahi P, Piluso A, et al. Hepatitis C virus syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. *World J Hepatol* 2015;7:327-43.

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23. Hu F, Yan Z, Ma B, Jiang Y, Huang H. The impact of concurrent Hashimoto thyroiditis on thyroid nodule cytopathology assessed by ultrasound-guided fine-needle aspiration cytology. *Postgrad Med* 2020;132:506-11.
 24. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. *Autoimmun Rev* 2014;13:391-7.
 25. Harvey AM, Truong LD, Mody DR. Diagnostic pitfalls of Hashimoto's/lymphocytic thyroiditis on fine-needle aspirations and strategies to avoid overdiagnosis. *Acta Cytol* 2012;56:352-60.
 26. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1-133.
 27. Shimizu K, Nakajima Y, Kitagawa W, Akasu H, Takatsu K, Ishii R, et al. Surgical therapy in Hashimoto's thyroiditis. *J Nippon Med Sch* 2003;70:34-9.
 28. Abbasgholizadeh P, Naseri A, Nasiri E, Sadra V. Is Hashimoto thyroiditis associated with increasing risk of thyroid malignancies? A systematic review and meta-analysis. *Thyroid Res* 2021;14:26.
 29. Chen AY, Bernet VJ, Carty SE, Davies TF, Ganly I, Inabnet WB 3rd, et al. American Thyroid Association statement on optimal surgical management of goiter. *Thyroid* 2014;24:181-9.
 30. Alnefaie SM. Surgical Decision-Making in Thyroiditis: A Review Article. *Cureus* 2023;15:e46055.