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REVIEW

A Review of Testing for Distinguishing Hashimoto's Thyroiditis in the Hyperthyroid Stage and Grave's Disease

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Abstract: Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two very common autoimmune thyroid diseases (AITD). In this review, we use "HT in the hyperthyroidism stage" to refer to early HT with clinical manifestations of hyperthyroidism. In clinical practice, it is not easy to distinguish between HT in the hyperthyroidism stage and GD as they exhibit very similar clinical symptoms. The current literature lacks so far studies that systematically compare and summarize hyperthyroidism due to HT and GD from varied aspects. It is necessary to focus on all the clinical indices of HT in the hyperthyroidism stage and GD, for accurate diagnosis. Multiple databases such as PubMed, CNKI, WF Data, and CQVIP Data were used to search the literature concerning HT in the hyperthyroidism stage and GD. The information extracted from the relevant literature was summarized and further analyzed. To differentially diagnose hyperthyroidism as HT or GD, it is recommended to first focus on serological tests, followed by imaging tests, as well as the thyroid I131 uptake index. In pathology, fine needle aspiration cytology (FNAC) is the gold standard for the differential diagnosis of HT and GD. Test results from cellular immunology and genetics could also be used to accurately diagnose between the two diseases, which may be further developed and studied in the future. In this paper, we reviewed and summarized the difference between HT in the hyperthyroidism stage and GD from the following six aspects: blood tests, imaging, thyroid I131 uptake, pathology, cellular immunology, and genetics.

Keywords: Hashimoto's thyroiditis, Graves' disease, diagnosis, differential diagnoses

Introduction

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the most common autoimmune thyroid diseases (AITD) in clinical practice. The etiology of HT is the destruction of thyroid follicular cells directly caused by apoptosis. At the initial stage of HT, a small amount of thyroid follicular cells are destroyed, and the thyroid hormone in the destroyed cells is released. The patient may have temporary hyperthyroidism symptoms. With the development of the disease, a large number of thyroid follicular cells are destroyed, and the thyroid cannot produce enough thyroxine. The patient may gradually develop hypothyroidism symptoms. Based on the patients' thyroid functionality, HT can be divided into three phases: hyperthyroidism HT, normal thyroid HT, and hypothyroidism HT. In this review, we ues "HT in the hyperthyroidism stage" to refer to early HT with clinical manifestations of hyperthyroidism. The etiology of GD consists of thyroid-stimulating antibodies (TSAb) and the thyroid-stimulating hormone (TSH) competitively combining with the alpha subunit of the thyroid-stimulating hormone receptor (TSHR). The adenylate cyclase signaling system is then activated, leading to hyperplasia of the thyroid follicular epithelial cells, resulting in the excessive production of thyroid hormones. The stimulation of the TSHR by TSH is controlled by a negative-feedback regulation of the hypothalamic-pituitary-thyroid axis. Thus, thyroid hormone production is kept in balance. However, there is no such control mechanism when TSAb stimulate the TSHR, leading to thyroid hyperplasia and hyperfunction.[1] Therefore, TSAb are considered the pathogenic antibodies of GD. All GD patients show hyperthyroidism, so only HT in the hyperthyroidism stage needs to be differentiated from GD. HT and GD are both AITD,[2] sharing a common

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genetic background, allowing the possibility of mutually converting. During their hyperthyroidism phase, they exhibit very similar clinical symptoms, and are difficult to be distinguished. It is thus necessary to focus on all the clinical indices of hyperthyroidism of HT and GD, to allow for an accurate diagnosis. In this study, we reviewed and summarized the differences between HT in the hyperthyroidism stage and GD regarding the following six aspects: blood tests, imaging, thyroid I131 uptake, pathology, cellular immunology, and genetics.

Methods for Diagnosis

The clinical data of HT in the hyperthyroidism stage and GD are summarized in Table 1. The data are categorized into blood tests, imaging, thyroid I131 uptake and pathology.

Blood Tests

When it comes to blood tests, the commonly used indices relating to thyroid functions are TSH, thyroxine (TT_4), triiodothyronine (TT_3), free thyroxine (FT_4), free triiodothyronine (FT_3), the thyrotropin receptor antibody (TRAb), the thyroid eroxidase Antibody (TPOAb), and the anti-thyroid auto-antibodies (TgAb). The TSH level is the most sensitive index to reflect thyroid functionality. The FT_4 and FT_3 are the main hormones that play a role in achieving the biological effects of the thyroid. For most patients, hyperthyroidism is accompanied by high TT_4 and TT_3 levels. In some cases, the

Table 1 Comparison of Differential Diagnosis Indices for HT in the Hyperthyroidism Stage and GD

Tests		**Hashimoto's Thyroiditis in the Hyperthyroidism Stage (HT)**	**Graves' Diseases (GD)**
Blood tests	TRAb (U/L)	Increase	Significant increase, 10x the normal value (on the average)
	TgAb (U/L)	Significant increase, 30x the normal value (on the average)	Increase
	TPOAb (U/L)	Significant increase	Increase
Imaging	Echogenic features in the thyroid	Focal reduced echogenicity Nodular-like Diffusely reduced echogenicity Diffusely enhanced echogenicity	Focal reduced echogenicity Diffusely reduced echogenicity Echo of the parenchyma thickened
	Blood flow distribution in the thyroid	Grade II-III	Grade III (Thyroid inferno)
	PSV (cm/s)	Increase	Significant increase
	EDV (cm/s)	Increase	Significant increase
	%AREA	Relatively high	Relatively low
	MEAN	Relatively low	Relatively high
	Lymph nodes around the thyroid	Lymph nodes in cervical areas V and VI	N/A
1131	Thyroid 1131 uptake rate	Increase Suppressed by T3	Significant increase Not suppressed by T3
	Thyroid iodine conversion rate	N/A	Peak moving forward
Pathology	FNAC	Diffuse lymphocytic infiltration Formation of germinal centers Enlarged epithelial cells Enlarged nuclear volume Eosinophilic cytoplasm formation (Askanazy or Hurthle cells)	High columnar epithelial cells Abundant cytoplasm, cytoplasmic vacuoles, and minimal colloid infiltration of lymphocytes/plasma cells Glandular epithelial cells without atrophy or degeneration

Abbreviations: PSV, the peak systolic velocity; EDV, the end diastolic velocity; %AREA, the area ratio of low-strain region; MEAN, the average relative value; FNAC, fine needle aspiration cytology.

TT_3 level may increase earlier than the TT_4. As a summary, all four indices, TT_4, TT_3, FT_4, and FT_3, could be used to diagnose hyperthyroidism. Regarding blood tests, HT and GD patients are diagnosed to be in the hyperthyroidism phase when there is presence of a low level of TSH, and high levels of TT_4, TT_3, FT_4, and FT_3. After confirmation of hyperthyroidism, it is helpful to test for thyroid autoantibodies to differentiate between HT and GD. Recently, the American Thyroid Association Issues updated their guidelines for hyperthyroidism. In addition, the Endocrinology Society of the Chinese Medical Association formulated guidelines for hyperthyroidism in China in 2012. These societies concluded that serum TSH and FT_4 levels are the most relevant indicators for the diagnosis of GD hyperthyroidism. The amount of TRAb can be used to determine the etiology of hyperthyroidism.[3] In fact, TRAb, which is also known as TSH binding inhibitory immunoglobulin, has become nowadays the No.1 indicator to diagnose GD. TRAb is tested for through the electrochemiluminescence immunoassay method, and a TRAb>1.75 IU/L is considered positive. GD patients who have not yet been treated show positive rate of 98%.[4] Based on clinical examples found in the literature, GD patients show significantly higher serum TRAb levels than HT patients.[5] During outbreak periods, GD patients show obvious higher positive rates and serum TRAb levels than healthy individuals. During remission, the indice drop. Therefore, TRAb levels are highly valuable in the diagnosis of GD. In fact, they can be used as a specificity index for GD diagnosis, playing a significant role in predicting GD recurrence.[6] Compared to TRAb, the Thyroid Stimulating Antibody (TSAb) not only binds to the TSH receptor but also stimulates the thyroid cells. Approximately 85–100% newly diagnosed GD patients show positivity for TSAb, with its average activity at 200%-300%. After binding with the TSH receptor, TSAb directly increases the level of adenosine 5′-monophosphate in the cells.[7] Furthermore, TSAb induces oxidative stress directly in GD patients.[8] TPOAb and TgAb are nonspecific antibodies to the thyroid and are both the most meaningful indicators for diagnosing HT. Laboratory test results reveal that HT patients show positivity for both TPOAb and TgAb with significantly elevated levels.[9] Both HT and GD patients show higher than normal serum TPOAb and TgAb levels. However, HT patients show more obvious elevation in the levels of these entities. This indicates that TPOAb and TgAb play an important role in the pathogenesis and diagnosis of HT.[6] According to the available HT and GD diagnostic models, GD patients show significantly higher levels of TRAb than HT patients, while HT patients show significantly higher levels of TgAb than GD patients. This is highly valuable for distinguishing between HT and GD patients in their early phase of hyperthyroidism.[10] There are clinical case studies using medians (interquartile range), with a normal serum TRAb level of 0.30 (0.00) IU/L, TPOAb 23.30 (9.31) IU/mL, and TgAb 10.00 (1.65) IU/mL. The level of TgAb in the blood of HT patients significantly increased, reaching an average of about 30 times the normal value, while the level of TRAb in the blood of GD patients significantly increased, reaching an average of about 10 times the normal value.[11,12]

Imaging

In imaging, ultrasonography is the most commonly used auxiliary examination for the diagnosis of hyperthyroidism in HT and GD. HT patients show diffusely swollen or a nodular thyroid, with uneven echo, while GD patients show a diffuse or focal reduced echogenic, with accelerated blood flow signaling in the reduced echogenic area. Recently, the differential diagnosis based on imaging also depends on the peak systolic velocity (PSV) cutoff value and ultrasonic elastography parameters. Some other ultrasonography indices include thyroid size (both lateral lobes thickness, length, width, and isthmus thickness), echogenic features of the thyroid, blood flow distribution in the thyroid, the superior thyroid artery blood flow rate, and the presence or absence of swollen lymph nodes around the thyroid. Based on the Handbook of Modern Diagnostic ultrasonography, a swollen thyroid could be confirmed if one or more of the below three indices is confirmed: lobe width $\geq$ 25 mm, lobe thickness $\geq$ 20 mm, and isthmus thickness $\geq$ 5 mm. HT patients show a larger than normal thyroid in all four aspects. Specifically, during the hyperthyroidism phase, the lobe length increase is more obvious than during other phases.[13] Ultrasonography features of HT are very diverse and can be categorized into four types: focal reduced echogenic, nodular-like, diffusely reduced echogenic, and diffusely enhanced echogenic. A correlation exists between these thyroidal echo characteristics and the clinical progression of HT.[14] In the early stages of HT, the follicular cells are mildly destructed, and the inflammation area is very small. Thus, the echo is characterized by patchy irregular hypoechoic areas, with the rest of the thyroid parenchyma exhibiting normal echogenicity. As the disease progresses, areas of inflammation exhibit "nodular-like" echoes, which are randomly scattered or diffusively distributed. There is not an obvious tumor, but rather diffuse echogenic abnormalities with multiple nodules. Multiple or single nodules could be seen on a normal thyroid background. When the

follicular cells are continuously destroyed, the "nodule-like" areas gradually increase and aggregate into schistose. The echo is then characterized with diffusely reduced echogenicity, in addition to a diffusive reticular septum and a diffused patchy reduced echogenicity. During the recovery period in HT, as the inflammation subsides, the inflamed area gradually decreases or disappears, and the thyroidal echo enhances.[15–17] The increased blood flow signal in the hyperthyroidism phase of HT is characterized as a grade II and III.[13] The ultrasonography observations of GD are clearer than those of HT. Varying degrees of a diffusely swollen thyroid can be observed in most GD patients. The thyroidal echogenicity is characterized as diffusive or focally reduced echogenic areas. The echo of thyroid parenchyma can be thickened. The thyroid blood flow signal is very strong, characterized as grade III, also known as 'thyroid inferno.' Concerning the superior thyroid artery spectral Doppler parameters, PSV is the most useful parameter in discriminating between HT and GD. PSV reflects thyroid blood flow status, while the end diastolic velocity (EDV) reflects the thyroid blood perfusion status. The PSV of both HT and GD patients is significantly higher than normal levels. Specially, the PSV and EDV of GD patients increase much higher than those in HT patients. Based on clinical case studies, researchers claim that the optimal critical value of the PSV is 54.3 cm/s. If the PSV is higher than 84.92 cm/s, GD can be diagnosed.[18] In addition, some researchers use a critical value of PSV of 50.5 cm/s for the discrimination between GD and thyroiditis.[19] In China, the optimal critical value of the PSV is 45.25 cm/s and is used to identify GD.[20] Two other studies from Japanese populations reported a PSV diagnostic threshold value of 45 cm/s and 43 cm/s, respectively, for the discrimination between GD and destructive thyroiditis.[21,22] These differences among the critical values of PSV to be used as cut-off values to diagnose GD might come from race-related differences. Furthermore, when discussing the elastic parameters, the area ratio of low-strain region (%AREA) and the average relative value (MEAN) can also be used to distinguish between HT and GD. The %AREA index of GD patients is lower than that of HT patients, and the MEAN index is higher than that of HT patients.[23] In addition, the detection of lymph nodes in the V and VI cervical areas could also be an indicator for the diagnosis of HT, especially when it comes to the hyperthyroid phase of HT.[24]

Thyroid I131 Uptake

HT patients show increased thyroid I131 uptake rate during the hyperthyroid state, which could be suppressed by T_3. GD patients show even higher thyroid I131 uptake rate, which cannot be inhibited by T_3. Some GD patients have increased iodine turnover in the thyroid, along with a peak moving forward phenomena. The thyroid I131 uptake rate is an important factor to assess thyroid function, in addition to being a traditional way to diagnose hyperthyroidism.[25] The iodine absorption rate curve can accurately and objectively describe the pattern of thyroid tissue absorption of radioactive iodine. The 24-h maximum iodine absorption rate is usually used clinically to represent the iodine absorption function of patients with hyperthyroidism. The normal value of thyroid I131 uptake rate (the Geiger counter test) is 5–25% in 3 h, and 20–45% in 24 h. The peak appears at the 24th h. The T3 suppression test could be used to establish a differential diagnosis of patients with elevated iodine uptake. Thyroid hormone release in healthy subjects is controlled by the negative-feedback-regulation from the hypothalamic-pituitary-thyroid axis. When the blood T_3 level increases, through the negative-feedback mechanism, the thyroid I131 uptake rate will decrease. This is called the T_3 suppression. Based on established clinical diagnostic models of patients with hyperthyroidism, the test results of thyroid function, thyroid antibodies, and radioactive iodine uptake are summarized in the literature.[26] It has been suggested that the radioactive iodine uptake at 2h, 6h and 24h in the GD group was significantly higher than that in the HT group. The area under the curve of iodine absorption rate in the GD group was significantly larger than that in the HT group. As for the thyroid iodine uptake rate, it has increased in GD patients. In fact, the iodine uptake rate increases rapidly in the early stage, and keeps increasing steadily with time, till it peaks around the 24th h. In some GD patients, the iodine conversion rate in the thyroid increases, and its peak moves forward.

Pathology

Fine needle aspiration cytology (FNAC) is the golden standard for diagnosis of HT and GD. The histopathology of HT demonstrates diffuse lymphocytic infiltration, the formation of germinal centers, nuclear volume enlargement, an eosinophilic cytoplasm (Askanazy or Hurthle cells) appearing in enlarged epithelial cells, as well as thyroid interstitial fibrosis at different levels. Furthermore, epithelioid granulomas, multinucleated giant cells, plasma cells, and normal follicular epithelial cells can also sometimes be observed. The histopathology of GD demonstrates high columnar epithelial cells, an abundant cytoplasm,

cytoplasmic vacuoles, and minimal colloid. There may also be infiltration of lymphocytes or plasma cells of varied degrees, along with glandular epithelial cells without atrophy or degeneration.[10,27–30]

Future and Prospects: Cellular Immunology and Genetics

In cellular immunology, the helper T cell Th1/Th2 cell balance and Th17/CD4+T cell percentages differ between HT and GD patients. Similarly, in genetics, the gene codons and gene frequencies differ between HT and GD patients. The above differences have huge research prospects and diagnostic values, and will help in the differential diagnosis of HT and GD in the future. Details are summarized in Table 2.

Th1 and Th2 are effector T cells. They also have immunomodulatory effects. Interferon-γ (IFN-γ) produced by Th1 can activate the expression of intracellular Th1 subset-specific transcription factor T-bet. T-bet can promote IFN-γ gene transcription and inhibit interleukin-4 (IL-4) gene transcription. On the contrary, Th2-produced IL-4 activates the Th2 subset-specific transcription factor Gata-3. The latter promotes IL-4 gene transcription and inhibits IFNG gene transcription. As a result, Th1 and Th2 can regulate each other. The direct cause of thyroid follicle destruction in HT patients is thyroid cell apoptosis caused by Th1 cell-mediated immune damage. Infiltrating T cells and B cells in the patient's thyroid tissue express the ligand Fas-L with the pro-apoptotic protein Fas. Th1 cells release cytokines (IFN-γ, IL-2, tumor necrosis factor-α (TNF-α), etc.) under the stimulation of thyroid autoantigens. Cytokines stimulate the expression of Fas on the surface of thyroid cells. Binding of Fas and Fas-L leads to apoptosis of thyroid cells.[31] GD is considered as a Th2 skewed disorder. While early stages of the humoral immune response involve Th1 cytokines (eg IFN-γ), long-term immunity relies on IgG4 antibodies driven by Th2 cytokines (eg IL-4). During the first stage, antigen-presenting cells (APCs) and B-cell-derived cytokines (IFN-γ and TNF-α) stimulate thyroid cells to secrete various chemokines. These include the C-X-C motif chemokine 10 (CXCL10) that recruits Th cells. Th cells interact with B cells to produce antibodies. During the second stage, Th2 cells in the thyroid suppress Th1 responses by secreting IL-10, IL-5 and IL-4, thereby preventing thyroid destruction. At this stage, the thyroid may be protected from destruction by inhibiting macrophages (Th2 cytokines) and up-regulating anti-apoptotic mechanisms (BCL-XL) or down-regulating FasL-Fas ligand interaction. Concurrently, increased Th2 responses lead to increased antibody production.[32] During the 9th National Academic Conference of Immunology, some researchers pointed out that, the expression levels of IFN-γ and IL-4 mRNA in peripheral blood of GD patients were significantly decreased. The expression level of transcription factor T-bet mRNA in this population has a downward trend when compared with healthy people. It is closely related to the imbalance of Th1/Th2 cell balance. Th17 secretes IL-17, IL-21, IL-22, IL-26, TNF-α and other cytokines. These cytokines act on a variety of immune or non-immune cells to play an immunomodulatory role. Thus, Th17 plays an important role in the occurrence and development of immune pathological damage, especially autoimmune diseases. Both HT and GD patients show increased percentages of Th17/CD4+ T cells in peripheral blood, and HT patients show even higher percentages than GD patients. Meanwhile, the percentage of Th17/CD4+ T cells in peripheral blood of HT patients is significantly positively correlated with the serum level of TgAb, thus showing a correlation with the serological test results previously mentioned. The increased percentages of Th17/CD4+ T cells can be used as one of the diagnostic criteria for HT and GD.[33] Different AITD susceptibility loci exist in CD40, and each locus has a different impact on the onset and development of AITD. In the Chinese population, the C64610G polymorphism locus was sequenced and analyzed by PCR technology, and it was found that the C/G genotype of HT patients was significantly

Table 2 Comparison of Cellular Immunology and Genetic Test Indices for HT and GD

Tests		Hashimoto's Thyroiditis (HT)	Graves' Diseases (GD)
Cellular immunology	Helper T cell changes Th17/CD4+T cell percentages	Th1-mediated immune damage Significant increase	Th2 skewed disorder Increase
Genetics	CD40 polymorphism	C/G genotype significantly higher than normal level	Significantly increased genotype frequencies of CD40-1 C/C genotype and C allele

higher than the normal level. Furthermore, the genotype frequencies of CD40-1 C/C genotype and C allele in GD patients were significantly higher than normal levels.[34]

The Switch Between GD and HT

HT and GD are both AITD,[2] sharing a common genetic background, allowing the possibility of mutually converting. Although the probability is low, timely adjustment of the treatment plan for patients after conversion has a great impact on their prognosis. Therefore, timely detection of the transformation between the two and ensuring follow-up are extremely important.[35]

According to several published case reports, the conversion of GD to HT after treatment is indeed present. When GD patients undergo a significant transition from classic symptoms of hyperthyroidism (weight loss, palpitations, excessive sweating, tremor, and nervousness, etc.) to classic symptoms of hypothyroidism (weight gain and asthenia, etc.), and when the previously enlarged thyroid gland of GD patients becomes smaller and atrophied, additional examination can be conducted to determine whether there is a possibility of transitioning to HT. For example, TPOAB level is an excellent test item. Before adding an inspection, it is necessary to clarify (Please rule out the following situations before confirming the conversion of the disease): Treatment options for GD include antithyroid drugs, radioiodine therapy, and surgery. The occurrence of hypothyroidism in GD patients may be caused by surgical treatment (thyroidectomy with excessive resection range) or radioactive iodine therapy (excessive ionizing damage and tissue necrosis leading to excessive reduction in thyroid volume). However, the pathogenesis of HT following GD has not been confirmed. The most plausible one is the simultaneous presence of both blocking and stimulating antibodies. TRAb includes two types, one is stimulatory antibody (TSAb), and the other is inhibitory antibody (Thyroid stimulating blocking antibodies, TSBAb). The alterations in thyroid function are related to the balance in the activity of TRAb and TSBAb. In patients with GD, it was demonstrated that antithyroid drugs may lower the TRAb level. In patients who have coexisting stimulating and blocking antibodies, decreased TRAb level may increase the action of TSBAb, which eventually causes HT.[36,37] According to Padmanaban P, patients who refuse definitive therapy (thyroidectomy or radioiodine therapy), management of euthyroid state becomes challenging requiring frequent thyroid function tests and close follow-up.[38] Similarly, HT can also be converted into GD, but with a lower probability of occurrence. GD should be suspected when HT patients develop thyrotoxic symptoms that do not improve after reducing or stopping levothyroxine. The diagnosis relies upon good history and physical exam followed by supportive antibody titers and radioiodine uptake scan.[39] Continuous evaluation of TSAb levels is recommended in HT, particularly in cases of TSAb-positive and those under replacement, since it may help predict conversion to GD.[40] Distinct immune paradigms, paucity of functioning tissue in long-standing HT, and infrequent conversion of blocking (TSBAb) to stimulating (TSAb) thyrotrophin receptor antibody (TRAb) may account for this.[41] In addition, overall, the required course of disease for transitioning from HT to GD is longer than that for transitioning from GD to HT.

Conclusions

In clinical practice, the differential diagnosis of HT in the hyperthyroidism stage and GD should first focus on serological examinations, and second on imaging examinations, combined with thyroid I131 uptake rate and other indicators. In terms of blood tests, both HT in the hyperthyroidism stage and GD patients may be diagnosed as hyperthyroid. After confirmation of hyperthyroidism, testing for autoantibodies against the thyroid can help in differentiating between HT in the hyperthyroidism stage and GD. The level of TgAb in the blood of HT in the hyperthyroidism stage patients increases significantly, to about 30 times of the normal value, while the level of TRAb in the blood of GD patients increases significantly, to about 10 times of the normal value. In terms of imaging, ultrasonography is the most commonly used auxiliary examination for the diagnosis of HT in the hyperthyroidism stage and GD. HT patients show diffuse or nodular swollen thyroid, with uneven echogenicity. GD patients show diffuse or focal thyroid reduced echogenic, and significantly accelerated blood flow signal at the reduced echogenic area. During recent years, the differential diagnosis through imaging also depended on the PSV cutoff value, ultrasound elasticity parameters, and the presence or absence of swollen lymph nodes around the thyroid. Thyroid I131 uptake is increased in HT in the hyperthyroidism stage patients and can be inhibited by T_3. Thyroid I131 uptake rate is significantly increased in GD patients and cannot be suppressed by T_3. The iodine conversion rate in the thyroid gland of some GD patients increases rapidly, and the peak is shifted forward. In terms of pathology, FNAC is the gold standard for the diagnosis of HT and GD. The histopathology of

HT is diffuse lymphocytic infiltration, formation of germinal centers, increased nuclear volume within enlarged epithelial cells, and eosinophilic cytoplasm (Askanazy or Hürthle cells). The histopathological manifestations of GD are tall columnar epithelial cells with abundant cytoplasm, cytoplasmic vacuoles, and few glia, with varied degrees of lymphocyte or plasma cell infiltration, but no atrophic degeneration of glandular epithelial cells. In clinical practice, when patients with symptoms of hyperthyroidism need to be diagnosed, thyroid hormone levels examinations (TSH, TT_3, TT_4, FT_3, and FT_4) and iodine uptake rate testing should be performed first. Meanwhile, ultrasound is also used as a routine examination before diagnosing hyperthyroidism in patients. After the diagnosis of hyperthyroidism, if the cause needs to be determined, thyroid related antibodies should be tested, including TRAb, TPOAb and TgAb. Other imaging examinations besides ultrasound should only be increased when necessary. When performing routine ultrasound examination, if the patient has thyroid nodules, the report will give TIRAD (Thyroid imaging reporting and data system) grading based on the morphology of the nodules. If TIRAD grading is found to be higher than or equal to level 4, FNAC should be added to prevent missed diagnosis of hyperthyroidism combined with thyroid cancer. In terms of cellular immunology, helper T cell Th1/Th2 cell balance and Th17/CD4+ T cell percentage distribution differ between HT and GD patients. In terms of genetics, there are differences in gene codons and gene frequencies between HT and GD patients. These differences mentioned above have great research prospects and diagnostic value, which will help in the differential diagnosis of HT in the hyperthyroidism stage and GD in the future. In addition, HT and GD are both AITD, sharing a common genetic background, allowing the possibility of mutually converting. Considering that adjusting the treatment plan after patient conversion has a significant impact on their prognosis, it is extremely important to promptly detect the transition between the two and ensure follow-up.

Ethics Standards

This article does not contain or involve any human participants and/or animals.

Informed Consent

For this type of study formal consent was not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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