RESEARCH

Clinical differences between IgG4 Hashimoto's thyroiditis and primary thyroid lymphoma

Liyuan Liu[1], **Yang Yu**[1], **Lei Chen**[2], **Yang Zhang**[1], **Guizhi Lu**[1], **Ying Gao**[1] and **Junqing Zhang**[1]

[1]Department of Endocrinology, Peking University First Hospital, Beijing, People's Republic of China
[2]Department of Ultrasound, Peking University First Hospital, Beijing, People's Republic of China

Correspondence should be addressed to Y Gao: gaoyingpkufh@bjmu.edu.cn

Abstract

Background: Hashimoto's thyroiditis (HT) can be divided into IgG4 HT and non-IgG4 HT based on IgG4 and IgG immunohistochemical staining. In clinical practice, it is often necessary to identify diseases such as primary thyroid lymphoma (PTL) and IgG4 HT when a patient presents with a rapidly enlarged thyroid. The aim of our study was to uncover the differential points between the two diseases.
Methods: Clinical information from 19 IgG4 HT and 10 PTL patients was obtained from the patients' medical records, including age, sex, main clinical manifestation, thyroid functional status, the presence of serum anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, and thyroid ultrasonography results. Thyroid sections from all patients were collected to detect IgG4 and IgG expression by immunohistochemical staining.
Results: The IgG4 HT patients were significantly younger than those in the PTL group (39.68 ± 10.95 vs 66.20 ± 10.23 years, $P < 0.001$). There were no significant differences in the sex distribution or TgAb- or TPOAb-positive rates. The PTL group had a higher prevalence of clinical hypothyroidism than the IgG4 HT group ($P = 0.016$). In the PTL group, thyroid lesions were more likely to exhibit hypoechogenicity (6/6 vs 1/19, $P < 0.001$) on ultrasound images. In the PTL group, two patients met the immunohistochemical cut-off value of the criteria for IgG4 HT.
Conclusions: Simply relying on immunohistochemistry for IgG4 cannot diagnose IgG4 HT correctly when a patient presents with rapid thyroid enlargement. A combination of clinical and pathological analyses will help distinguish IgG4 HT from PTL which may be with abundant IgG4-positive plasma cells.

Key Words

- IgG4 Hashimoto's thyroiditis
- primary thyroid lymphoma
- goitre
- clinical difference

Introduction

Hashimoto's thyroiditis (HT) is a common autoimmune thyroid disease characterized by goitre, lymphoplasmacytic infiltration of parenchyma, and positivity for serum antibodies specific to thyroid antigens (including thyroid peroxidase and thyroglobulin) (1). In 2009, Li *et al.* (2) first proposed dividing HT into IgG4 and non-IgG4 HT based on IgG4 and IgG immunohistochemical staining results in thyroid tissue and found that IgG4 HT had unique clinical, serological, sonographic, and histopathological features compared to non-IgG4 HT (3, 4). IgG4 HT can present as goitre, and sometimes the thyroid would become enlarged rapidly, leading to compressive symptoms, possibly requiring surgical removal (5, 6). With regard to thyroid function, IgG4 HT

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-21-0144

is associated with hypothyroidism (3). The diagnosis of IgG4 HT requires the exclusion of inflammatory disease, lymphoma, or other malignant tumours.

Primary thyroid lymphoma (PTL) is a type of lymphoma originating from the thyroid gland and is often complicated with HT. The main clinical manifestation of PTL is a rapidly growing neck mass that may cause compressive symptoms such as dysphagia, dyspnoea, and hoarseness (7, 8). Thus, patients with PTL or IgG4 HT may present with symptoms of goitre and hypothyroidism. Kentaro *et al.* (9) reported a case of PTL complicated with HT that was initially misdiagnosed with IgG4 HT. In clinical practice, it is often necessary to identify diseases such as PTL, undifferentiated carcinoma, and IgG4 HT when a rapidly enlarging thyroid occurs.

The purpose of this study was to compare the clinical features and immunohistochemical staining for IgG4 in IgG4 HT and PTL and to contribute to the differential diagnosis of diseases with goitre.

Materials and methods

Patients

A total of 19 patients with IgG4 HT were retrospectively enrolled at Peking University First Hospital from 2009 to 2014. Based on lymphoplasmacytic infiltration and interstitial fibrosis in haematoxylin and eosin (HE) staining and the immunohistochemistry analysis for IgG4 and IgG in our previous research (10, 11), the 19 patients were diagnosed with IgG4 HT using the cut-off value of more than 20 IgG4-positive plasma cells per high-power field (HPF) and an IgG4/IgG-positive plasma cell ratio greater than 30% (2, 12). All of these patients underwent thyroidectomy for nodular lesions suspicious of thyroid cancer. Based on postoperative pathological reports, we found that 17 HT patients (89.5%) had comorbid thyroid cancer and 2 were diagnosed with HT alone. The clinical data of all the patients were collected, and there was no evidence of other autoimmune diseases or other organs being affected by IgG4-related disease (IgG4-RD) according to the 2019 ACR/EULAR IgG4-RD criteria (13).

For comparison, the pathology laboratory information system was searched retrospectively to identify patients from 1995 through 2020, and the search yielded ten PTL patients with pathological samples. PTL was diagnosed by pathological examination after partial thyroidectomy ($n = 3$) or core needle biopsy ($n = 7$). The pathological diagnosis of PTL was based on morphology, immunohistochemistry, or/and flow cytometry (14). According to the 2016 World Health Organization (WHO) lymphoma classification, three patients had diffuse large B-cell lymphoma (DLBCL), four were diagnosed with mucosa-associated lymphoid tissue lymphoma (MALToma), one with small B-cell lymphoma, one with marginal-zone B-cell lymphoma, and one was identified with B-cell lymphoma without further pathotype. Based on clinical and pathological records, eight of the ten PTLs were diagnosed with HT.

Clinical information was obtained from the patients' medical records, including age, sex, clinical manifestation, and the results of thyroid function, thyroid antibody, and thyroid ultrasonography. None of the patients had evidence of hereditary or acquired variations in the concentration of thyroxine-binding globulin. The ultrasonographic examinations were performed by the conventional greyscale and colour Doppler, with 9–14 MHz linear transducers (Phillips iU22 and GE Logiq9). The thyroid sonographic characteristics of patients were described as follows: hypoechogenicity, heterogeneous, and normal echogenicity (3, 15). Hypoechogenicity was defined as an ultrasound signal significantly lower than normal thyroid tissue. Heterogeneous echogenicity is defined as the interweaving of low signal and normal tissue signal (3). Quantification was performed by two independent investigators in a double-blind manner. If there was any inconsistency, it will be resolved through negotiation.

This study complied with the Helsinki Declaration and was approved by the Ethics Committee of Peking University First Hospital. All the patients gave written informed consent.

Immunohistochemistry of IgG and IgG4 in thyroid tissues

Immunostaining for IgG and IgG4 was performed using the EnVision system (Dako Cytomation) as described in our previous studies (10, 11). Briefly, deparaffinated sections were treated with 3% hydrogen peroxide to inhibit endogenous peroxidase and were then blocked with 3% BSA. After preliminary treatment with 0.4% pepsin, the sections were incubated overnight at 4°C with the following primary antibodies: anti-IgG (rabbit polyclonal, GA042329, 1:1000; Gene Tech, Shanghai, China) and anti-IgG4 (mouse monoclonal, HP6025, 1:250; Southern Biotech, Birmingham AL, USA). The sections were then incubated with goat anti-mouse and anti-rabbit immunoglobulins conjugated to peroxidase-labeled dextran polymer (EnVision; Dako Cytomation). Tonsil tissue served as a positive control. Negative controls were

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-21-0144

prepared by incubating two sections with normal mouse IgG or normal rabbit IgG at the same dilution instead of the specific antibody. IgG4-positive or IgG-positive plasma cells were counted and averaged in five different HPFs (Olympus BX51T microscope, magnification ×400). The ratio of IgG4+/IgG+-positive plasma cells was also calculated in each case.

Two approaches were used to evaluate increased IgG4-positive plasma cells: (i) the cut-offs for IgG4-positive HT were >20 IgG4-positive plasma cells per HPF and a >30% IgG4/IgG-positive plasma cell ratio and (ii) the histological diagnostic criteria of IgG4-RD were >10 IgG4-positive plasma cells per HPF and a >40% IgG4/IgG-positive plasma cell ratio (16). Quantification was performed by two independent investigators in a double-blind manner.

Other pathological characteristics

The main pathological characteristics of IgG4 HT include interstitial fibrosis and lymphoplasmacytic infiltration (4, 17). The pathological results were analysed by pathologists from the Department of Pathology in our hospital to judge whether the PTL patients had these pathological characteristics.

Statistical analysis

Statistical analysis was performed using the SPSS v23.0 (SPSS) statistical package. For normally distributed data, the results are shown as the arithmetic mean ± s.d., and an unpaired *t*-test was performed. Data with a skewed distribution are summarized as the medians and interquartile ranges, and Mann–Whitney tests were performed to test for differences between the two groups; the chi-square test or Fisher's exact test was used for comparison of proportions between two variables. The level of significance was set at $P < 0.05$.

Results

Clinical features of all the patients

The clinical features of IgG4 HT and PTL are summarized in Table 1. All the PTL patients were older than 55 years. The patients in the IgG4 HT group were significantly younger than those in the PTL group (39.68 ± 10.95 vs 66.20 ± 10.23 years, $P < 0.001$). There were no significant differences in the sex distribution.

In terms of clinical manifestations, neck mass was the main clinical manifestation in both groups. Three patients in the PTL group even had compression symptoms such as dyspnoea and hoarseness, which were significantly higher than those in the IgG4 HT group. 3/19 patients in the IgG4 HT group also had similar B symptoms: two had a fever, sweats, or weight loss due to hyperthyroidism, and one presented with weight loss for unclear reasons. Thus, no obvious differences were found regarding the presence of B symptoms between the two groups ($P = 0.369$).

The PTL group had a higher prevalence of clinical hypothyroidism than the IgG4 HT group ($P = 0.016$).

Table 1 The clinical features of IgG4 Hashimoto's thyroiditis and primary thyroid lymphoma.

Groups	IgG4 HT (*n* = 19)	PTL (*n* = 10)	*P*-value
Age (years)	39.68 ± 10.96	66.20 ± 10.23	<0.001
Sex (male/female)	4/15	4/6	0.517
Clinical manifestations (*n*%)			
Neck mass	14 (73.7%)	10 (100.0%)	0.075
Compressive symptoms	0	3 (30.0%)	0.012
B symptoms	3 (15.8%)	3 (30.0%)	0.369
Hypothyroidism (*n*%)	3 (15.8%)	5 (50.0%)	0.128
Clinical	0	4 (40.0%)	0.016
Subclinical	3 (15.8%)	1 (10.0%)	1.000
Anti-Tg or Anti-TPO positive (*n*%)[a]	17/19 (87.5%)	7/8 (87.5%)	0.694
Anti-Tg	14 (82.4%)	5 (62.5%)	0.560
Anti-TPO	12 (70.6%)	5 (62.5%)	1.000
Sonographic features (*n*%)			
Thyroid sonographic characteristics[b]: normal echogenicity/hypoechogenicity/heterogeneous echogenicity	9/1/9	0/6/0	<0.001
Lymphadenopathy[c]	8/19 (42.1%)	7/9 (77.8%)	0.173

Values shown as the arithmetic mean ± s.d., median (25-75th percentile) or positive cases/total (%). Neck mass: found by physical examination, compressive symptoms: including dysphagia, dyspnoea, and hoarseness, B symptoms: including fever, night sweats, or weight loss.
[a]Only eight PTL had results of anti-thyroid antibodies. [b]Thyroid ultrasonography data were available for only six in the PTL group. [c]Only nine PTL patients had the results of cervical lymph nodes.
Anti-Tg, antithyroglobulin antibody; anti-TPO, anti-thyroid peroxidase antibody.

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-21-0144

Moreover, only eight PTL had results of anti-thyroid antibodies. Among them, seven patients had anti-thyroid antibodies (TgAb or TPOAb) positive and six of them were complicated with HT. The other with PTL alone was positive for TgAb. No significant differences were found in the TgAb/TPOAb-positive rate between the two groups, which may be related to the fact that most PTL patients with TgAb/TPOAb-positive (85.7% in our study) are complicated with HT.

For ultrasound images, only six PTL patients with HT had thyroid ultrasonography results, and all of them had hypoechogenicity. The lesions were more likely to appear hypoechogenic in the PTL group than those in the IgG4 HT group (6/6 vs 1/19, $P < 0.001$). The rate of cervical lymphadenopathy in the PTL group (7/9) was higher than that of the IgG4 HT group (8/19); however, no significance was found. All the eight patients with lymphadenopathy in the IgG4 HT group were complicated with thyroid cancer, and five of them were pathologically confirmed as lymph node metastasis, two patients had reactive lymph nodes, and the other did not receive lymph nodes biopsy.

Immunohistochemical findings and other pathological characteristics

According to HE and immunohistochemical results, all patients with IgG4 HT had lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells (Fig. 1A and B) and interstitial fibrosis, and no storiform fibrosis and obliterative phlebitis were observed. In the PTL group, diffuse lymphoid tissue or atypical lymphocytic hyperplasia and infiltration were observed, and three out of ten patients had interstitial fibrosis. One was complicated by HT with IgG4+ plasma cell infiltration, and the other two were negative for IgG and IgG4 in immunohistochemical staining. In the PTL group, according to the immunohistochemical results, two cases met the cut-off value of IgG4-positive plasma cells and IgG4/IgG-positive plasma cell ratio in the criteria for IgG4 HT (Fig. 1C and D), and three were in accordance with the cut-off value of the diagnostic criteria for IgG4-RD.

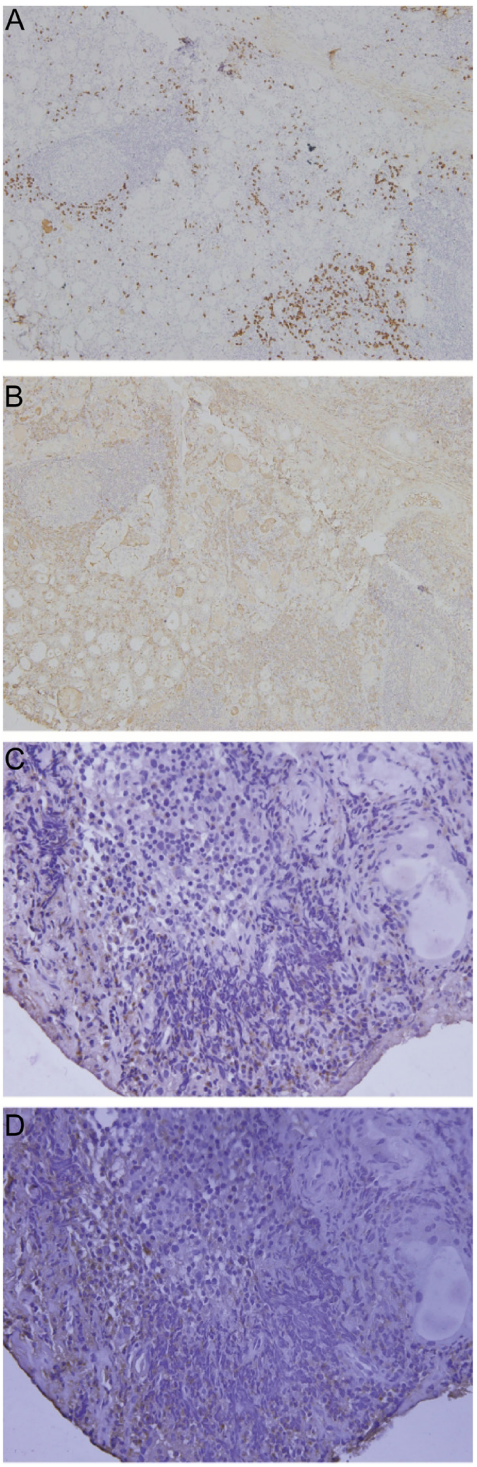

Figure 1
Immunohistochemistry and histopathological characterization of IgG4 HT and PTL cases. (A and B) Serial sections of the thyroid in a patient with IgG4 HT. There is diffuse infiltration of lymphoplasmacytic cells. Infiltration of IgG4-positive plasma cells (A) and IgG-positive plasma cells (B) are observed in IgG4 HT. (C and D) Serial sections of the thyroid in a PTL with HT case. Infiltration of IgG4-positive plasma cells (C) and IgG-positive plasma cells (D) are observed in PTL. Magnification ×100.

Discussion

Recent literature has reported a prevalence of IgG4 HT that varies from 12.6% to 42.4% (17). However, this result was based on the pathologic characteristics of the HT patients receiving thyroid operation. Since a coarse needle biopsy or surgery was not necessary for most HT patients,

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-21-0144

the true incidence of IgG4 HT may be much lower than previously reported. Patients with IgG4 HT have unique clinical manifestations (3, 10, 11, 18). Compared with non-IgG4 HT patients, IgG4 HT patients are younger, with a relatively high proportion of male patients. It is associated with subclinical hypothyroidism, which indicates that the disease course may progress more rapidly. IgG4 HT presents as goitre, and sometimes the thyroid enlarges rapidly, leading to compressive symptoms, which consequently results in a high rate of thyroidectomies as compared with non-IgG4 HT (5, 6, 19). They are more vulnerable to papillary thyroid carcinoma and may have worse clinical outcomes, including a larger tumour diameter and a higher percentage of lymph node metastasis (11).

PTL accounts for 1–5% of all malignancies of the thyroid gland (7), and it is reported that 78.8% of PTL patients are complicated with HT (20), which is consistent with the current study. PTL occurs most frequently in women (five times higher rate than in men) aged 50–80 years, which is similar to our study's results. Rapid enlargement of the thyroid gland, compression symptoms, and enlarged lymph nodes are the most common clinical symptoms of PTL.

Because the clinical manifestations, including goitre and compression, are similar in the two diseases and PTL is usually complicated with HT, PTL sometimes may be misdiagnosed as IgG4 HT. Kentaro *et al.* (9) reported that a patient with a previous history of HT mainly presented with a neck mass and dyspnoea, and blood examination revealed high serum IgG4 levels. After thyroid biopsy, the pathological findings showed dense lymphoplasmacytic infiltration with IgG4-positive plasma cells. Although IgG4 HT was suspected, treatment with glucocorticoid therapy was not predicted to be efficacious. In an *in situ* hybridization study, the lesion was finally diagnosed as MALToma. Similarly, two other cases were reported of thyroid lymphoma with IgG4-positive plasma cell infiltration combined with HT (21, 22). Therefore, discrimination of IgG4 HT and PTL is important due to the different treatment strategies and prognoses for these two diseases.

In this study, compared with PTL patients, IgG4 HT patients were younger. It is consistent with the report that the prevalence of PTL is low in patients younger than 40 years (7). Although most patients presented with neck masses, only the patients in the PTL group had neck compression symptoms. In our study, B symptoms (fever, sweats, or weight loss) were also found in the IgG4 HT group; thus, clinicians should examine thyroid function and discriminate the causes of malignant diseases when B symptoms appear in patients with goitre.

In terms of serologic tests, the PTL group was more likely to have clinical hypothyroidism than the IgG4 HT group. There was no significant difference in the positive rate of thyroid antibodies between the two groups, which may be related to the fact that PTL patients are often complicated with HT.

From the ultrasonic characteristics, the PTL group mostly showed hypoechogenicity, while the IgG4 group mostly showed normal echo and heterogeneous echogenicity. PTL often presents as hypoechoic lesions on ultrasound (7), which is related to the degree and consistency of tumour cell proliferation (23). Diffuse lymphoid tissue or atypical lymphocytic hyperplasia and infiltration can be seen in PTL, and consistent cellular morphology is a characteristic of PTL, which results in a small difference in internal acoustic impedance. In addition, high rates of lymphadenopathy were observed in the PTL group, but there was no significant difference between the two groups. It may be attributable to the fact that all the IgG4 HT patients with enlarged lymph nodes were complicated with thyroid cancer in our study. It has been reported that IgG4 HT is more prone to having PTC, and PTC patients with IgG4 HT are more likely to exhibit lymph node metastasis (11, 24). This phenomenon reduced the difference between IgG4 HT and PTL in lymphadenopathy.

For the immunohistochemical staining results, two patients (2/10) in the PTL group met the criteria for IgG4 HT. Furthermore, the diagnosis of three patients in the PTL group conformed to the cut-off value of the comprehensive diagnostic criteria of IgG4-RD. Therefore, it may be unreliable to diagnose IgG4 HT only based on IgG4 and IgG immunohistochemical staining results, and other diseases such as PTL are easily misdiagnosed as IgG4 HT. Apart from the infiltration of IgG4+ plasma cells, interstitial fibrosis is also an important pathological feature of IgG4 HT (17); however, interstitial fibrosis was also seen in PTL patients in this study.

The treatment regimens for the two diseases are quite different. A recent study found that in patients with IgG4 HT, glucocorticoid treatment could effectively relieve symptoms, but the size of the thyroid did not change significantly and levothyroxine treatment was still needed (25). Treatment options for PTL include chemotherapy, radiotherapy, and surgical intervention. Early diagnosis contributes to better management, which may lead to a better therapeutic effect and may reduce the number of radical surgical interventions. Misdiagnosis of the two diseases and inappropriate treatment may lead to treatment delays and adverse prognoses. Recently, a case

https://etj.bioscientifica.com
https://doi.org/10.1530/ETJ-21-0144

of IgG4-type multiple myeloma mimicking IgG4-related disease was reported, and the researchers proposed that patients with elevated IgG4 levels should undergo systemic examinations to rule out malignancies (26). It is necessary to closely integrate clinical symptoms and pathological characteristics to establish a correct diagnosis for patients with rapid goitre.

The study is retrospective and is thus subject to all of the inherent limitations of a retrospective study. Another limitation is the small number of patients analysed. However, PTL is a very rare disease, and it is difficult to obtain larger sample sizes. A multicentre, large-sample study may be needed to obtain more reliable results in the future.

In summary, in HT patients with an 'enlarged thyroid', diverse aetiologies, including IgG4 HT and PTL combined with HT, must be carefully considered. Infiltration of IgG4+ plasmocytes alone is not sufficient for the diagnosis of IgG4 HT. A combination of clinical and pathological analyses can help to distinguish it from PTL with abundant IgG4+ plasma cells.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81900711) and Capital's Funds for Health Improvement and Research (CFH 2018-2-4074).

Statement of ethics

This study was approved by the biomedical research ethics committee of Peking University First Hospital in compliance with the Declaration of Helsinki. Informed consent was exempted because of the retrospective nature of the study and minimal risk of harm to the study subjects.

Data availability statement

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of the research participants but are available from the corresponding author [Ying Gao].

Author contribution statement

Study design: Yang Yu, Ying Gao, Junqing Zhang. Material preparation and data collection: Liyuan Liu, Yang Zhang. Data analysis and investigation: Liyuan Liu, Lei Chen, Shuang Zhang, Guizhi Lu. Drafting of the manuscript: Liyuan Liu. Revision of the manuscript: Yang Yu, Ying Gao.

Acknowledgement

The authors are particularly grateful to all the people who have given us help with our article.

References

1 Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, de Vincentiis M & Greco A. Hashimoto's thyroiditis: an update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmunity Reviews* 2020 **19** 102649. (https://doi.org/10.1016/j.autrev.2020.102649)

2 Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, Nagayama K, Nakamura H & Kakudo K. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathology International* 2009 **59** 636–641. (https://doi.org/10.1111/j.1440-1827.2009.02419.x)

3 Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A & Kakudo K. Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based with and without IgG4-positive plasma cells. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 1309–1317. (https://doi.org/10.1210/jc.2009-1794)

4 Li Y, Zhou G, Ozaki T, Nishihara E, Matsuzuka F, Bai Y, Liu Z, Taniguchi E, Miyauchi A & Kakudo K. Distinct histopathological features of Hashimoto's thyroiditis with respect to IgG4-related disease. *Modern Pathology* 2012 **25** 1086–1097. (https://doi.org/10.1038/modpathol.2012.68)

5 Zhao Z, Lee YJ, Zheng S, Khor LY & Lim KH. IgG4-related disease of the thyroid gland requiring emergent total thyroidectomy: a case report. *Head and Neck Pathology* 2019 **13** 523–527. (https://doi.org/10.1007/s12105-018-0940-4)

6 Abo Salook M, Benbassat C, Strenov Y & Tirosh A. IgG4-related thyroiditis: a case report and review of literature. *Endocrinology, Diabetes and Metabolism Case Reports* 2014 **2014** 140037. (https://doi.org/10.1530/EDM-14-0037)

7 Pavlidis ET & Pavlidis TE. A review of primary thyroid lymphoma: molecular factors, diagnosis and management. *Journal of Investigative Surgery* 2019 **32** 137–142. (https://doi.org/10.1080/08941939.2017.1383536)

8 Stein SA & Wartofsky L. Primary thyroid lymphoma: a clinical review. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3131–3138. (https://doi.org/10.1210/jc.2013-1428)

9 Miki K, Orita Y, Sato Y, Sugitani I, Noyama M, Fuji S, Domae S, Nose S, Hamaya K, Yoshino T, *et al.* Mucosa-associated lymphoid tissue lymphoma of the thyroid with abundant IgG4-positive plasma cells. *Auris, Nasus, Larynx* 2013 **40** 587–590. (https://doi.org/10.1016/j.anl.2012.12.004)

10 Zhang J, Zhao L, Gao Y, Liu M, Li T, Huang Y, Lu G, Gao Y, Guo X & Shi B. A classification of Hashimoto's thyroiditis based on immunohistochemistry for IgG4 and IgG. *Thyroid* 2014 **24** 364–370. (https://doi.org/10.1089/thy.2013.0211)

11 Yu Y, Zhang J, Lu G, Li T, Zhang Y, Yu N, Gao Y, Gao Y & Guo X. Clinical relationship between IgG4-positive Hashimoto's thyroiditis and papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 1516–1524. (https://doi.org/10.1210/jc.2015-3783)

12 Li Y, Wang X, Liu Z, Ma J, Lin X, Qin Y, Nishihara E, Miyauchi A & Kakudo K. Hashimoto's thyroiditis with increased IgG4-positive plasma cells: using thyroid-specific diagnostic criteria may identify early phase IgG4 thyroiditis. *Thyroid* 2020 **30** 251–261. (https://doi.org/10.1089/thy.2019.0063)

13 Wallace ZS, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, Hart PA, Inoue D, Kawano M, Khosroshahi A, *et al.* The 2019 American College of Rheumatology/European League Against

Rheumatism classification criteria for IgG4-related disease. *Annals of the Rheumatic Diseases* 2020 **79** 77–87. (https://doi.org/10.1136/annrheumdis-2019-216561)

14 Zhu J, Ma J & Union for China Lymphoma Investigators of Chinese Society of Clinical Oncology. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma 2021 (English version). *Chinese Journal of Cancer Research* 2021 **33** 289–301. (https://doi.org/10.21147/j.issn.1000-9604.2021.03.01)

15 Yu Y, Yu N, Lu G, Li T, Zhang Y, Zhang J, Gao Y, Gao Y & Guo X. Hashimoto's thyroiditis with elevated serum IgG4 concentrations is not equivalent to IgG4 Hashimoto's thyroiditis. *Clinical Endocrinology* 2018 **88** 943–949. (https://doi.org/10.1111/cen.13596)

16 Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Kloppel G, Heathcote JG, Khosroshahi A, Ferry JA, *et al.* Consensus statement on the pathology of IgG4-related disease. *Modern Pathology* 2012 **25** 1181–1192. (https://doi.org/10.1038/modpathol.2012.72)

17 Yu Y & Gao Y. Progress in diagnosis and treatment of IgG4-related thyroiditis. *Chinese Journal of Practical Internal Medicine* 2019 **39** 321–324. (https://doi.org/10.19538/j.nk2019040103)

18 Jokisch F, Kleinlein I, Haller B, Seehaus T, Fuerst H & Kremer M. A small subgroup of Hashimoto's thyroiditis is associated with IgG4-related disease. *Virchows Archiv* 2016 **468** 321–327. (https://doi.org/10.1007/s00428-015-1893-6)

19 Rotondi M, Carbone A, Coperchini F, Fonte R & Chiovato L. DIAGNOSIS OF ENDOCRINE DISEASE: IgG4-related thyroid autoimmune disease. *European Journal of Endocrinology* 2019 **180** R175–R183. (https://doi.org/10.1530/EJE-18-1024)

20 Travaglino A, Pace M, Varricchio S, Insabato L, Giordano C, Picardi M, Pane F, Staibano S & Mascolo M. Hashimoto thyroiditis in primary thyroid non-Hodgkin lymphoma. *American Journal of Clinical Pathology* 2020 **153** 156–164. (https://doi.org/10.1093/ajcp/aqz145)

21 Nomoto H, Miyoshi H, Nakamura A, Nagai S, Shimizu C & Atsumi T. Potential importance of a histopathological analysis in thyroidal diseases with high serum IgG4 levels. *Internal Medicine* 2018 **57** 453. (https://doi.org/10.2169/internalmedicine.9507-17)

22 Tan CL, Ong YK, Tan SY & Ng SB. IgG4-positive extranodal marginal zone lymphoma arising in Hashimoto's thyroiditis: clinicopathological and cytogenetic features of a hitherto undescribed condition. *Histopathology* 2016 **68** 931–937. (https://doi.org/10.1111/his.12854)

23 Zhang XM, Nong L, Ran X & Li M. Clinic pathological and ultrasonographic features of primary thyroid lymphoma. *Zhonghua Yi Xue Za Zhi* 2017 **97** 2936–2939. (https://doi.org/10.3760/cma.j.issn.0376-2491.2017.37.013)

24 Tasli F, Ozkok G, Argon A, Ersoz D, Yagci A, Uslu A, Erkan N, Salman T & Vardar E. The role of IgG4 (+) plasma cells in the association of Hashimoto's thyroiditis with papillary carcinoma. *APMIS* 2014 **122** 1259–1265. (https://doi.org/10.1111/apm.12297)

25 Han X, Zhang P, Li J, Liu Z, Lu H, Luo X, Pan B, Lian X, Zeng X, Zhang W, *et al.* Clinical features and treatment efficacy for IgG4-related thyroiditis. *Orphanet Journal of Rare Diseases* 2021 **16** 324. (https://doi.org/10.1186/s13023-021-01942-x)

26 Funada M, Nakano K, Miyata H, Nawata A & Tanaka Y. IgG4-type multiple myeloma with diffuse enlargement of the thyroid requiring differentiation from IgG4-related disease. *Internal Medicine* 2020 **59** 711–714. (https://doi.org/10.2169/internalmedicine.3839-19)

Received in final form 1 April 2022
Accepted 22 April 2022
Accepted Manuscript published online 25 April 2022