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IGG4-POSITIVE PLASMA CELLS IN HASHIMOTO THYROIDITIS

IgG4-related disease or inflammation-related IgG4-positivity?

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Avainsanat: Thyroid gland; Hashimoto thyroiditis; IgG4/IgG; IgG4-related disease.

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IgG4-positive plasma cells in Hashimoto thyroiditis: IgG4-related disease or inflammation-related IgG4-positivity?

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Despite the interest of researchers in IgG4-related disease (IgG4-RD), many questions still remain unanswered regarding the thyroid gland. We aimed to clarify the relationship between IgG4-positive plasma cells and the histopathological pattern in the Hashimoto thyroiditis (HT) in a Finnish series. HT specimens (n = 280) were retrieved from the Department of Pathology, Fimlab Laboratories. After re-evaluation, 82 (29%) cases (72 females and 10 males, 52 ± 17 years) with significant fibrosis were selected. CD38, IgG and IgG4 positivity in plasma cells was evaluated by immunohistochemistry. Adjusted IgG4-positive plasma cells per HPF > 20 and IgG4- to IgG-positive plasma cell ratio > 30% were adopted as threshold criteria and related to other morphological features. IgG4-positive HT group included 13 cases (15% from fibrotic HT, 4.6% from all HT, 50 ± 15 years, 11 females) with adjusted HPF count 30 ± 5 (23–40) IgG4-positive cells. IgG4-positivity significantly correlated with the presence of lobulation, oncocytic metaplasia and certain type of fibrosis, fibrosis spread outside the gland, lymphocytes/plasma cells epithelial penetration, the predominance of microfollicles and follicular atrophy in the present study. Despite the persisting uncertainty whether HT is IgG4-RD, HT with IgG4-positive plasma cells is histopathologically distinct entity with some geographic variability.

Key words: Thyroid gland; Hashimoto thyroiditis; IgG4/IgG; IgG4-related disease.

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Chronic lymphocytic thyroiditis was described in 1912 by Hakaru Hashimoto (1), and nowadays, this autoimmune disease is often called Hashimoto thyroiditis (HT). The major clinical findings are thyroid enlargement, hypothyroidism and the elevation of thyroid antibodies, namely thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb). Histopathological changes include diffuse lymphoplasmacytic inflammation including lymphoid follicles with germinal centres, damage and atrophy of thyroid follicles, oncocytic and rarely squamous metaplasia and variable amount of fibrosis (2). Fibrosis is more profound in fibrous variant of HT (FVHT) described by Katz and Vickery in 1974 (3).

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disorder described in almost every organ with the first description in a pancreas in 2001 and as a systemic entity in 2003 (4, 5). Clinically, it is frequently characterized by a mass formation mimicking tumour or lymphoma, multifocal mode, relapses and remissions, and response to the steroid therapy. Histology is the mainstay in the diagnostics of IgG4-RD. A dense lymphoplasmacytic infiltration, a storiform progressive fibrosis, and an obliterative phlebitis are IgG4-RD microscopical characteristics (6, 7). An elevated tissue IgG4

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concentration defined either as a number of IgG4 positive plasma cells or IgG4/IgG ratio in the organ specimen is organ and specimen type specific (8, 9).

Nevertheless, the presence of IgG4-positive plasma cells without accompanying histopathology can lead to overdiagnostics as IgG4-positive cells were described in a wide range of inflammatory and lymphoproliferative disorders (10-15). In addition, a raised serum IgG4 level is neither necessary nor adequate for the diagnosis (16, 17).

In the thyroid gland, Riedel thyroiditis (RT) has been proven both by morphology and IgG4 immunohistochemistry to be part of IgG4-RD spectrum (18, 19). Despite difficulties in distinguishing between RT and FVHT, there is an extrathyroidal extension of fibrosis, an obliterative phlebitis and a lack of oncocytic metaplasia in RT as diagnostic differentiation hallmarks (17, 18).

HT-related IgG4-positive cells were pioneered by Li et al. in 2009 (20) with following profound histopathological, clinical, imaging and laboratory characterization by the same authors (21-23). Non-Asian studies on IgG4-related HT are sparse (24-26). Notably, geographic, genetic and dietary (iodine) variation was described in HT cohort (27). Raess et al. revealed overlapping between HT and IgG4-RD, but no correlation of IgG4-positive plasma cells and IgG4-RT histopathological features (25).

Whether HT is a part of IgG4-RD spectrum remains to be clarified as well as relation to FVHT. In the light of previous studies, we focused on IgG4-positivity and IgG4-RD histopathological features in a series of thyroid gland surgical specimens with HT in the Finnish cohort in a university hospital setting. It is the second European and the first Nordic cohort focusing on IgG4-positivity in HT.

MATERIALS AND METHODS

Study cohort

In total, 280 cases with HT were found from the laboratory information system of the Department of Pathology, Fimlab Laboratories, Tampere, Finland from January 2011 to December 2017 (7-year-period). After re-evaluation by an experienced thyroid pathologist, 82 (29%) cases with significant fibrosis were selected for the study. The HT data set included 72 females (88%) and 10 males (12%). The mean age of patients was 52 ± 17 (ranged 12–85) years. Cases with RT were excluded from the study.

Clinically, the reasons for surgical treatment were as follows: goitre (n = 37 (45%)), malignancy (or suspicion) (n = 37 (45%)), thyrotoxicosis (n = 3 (4%)), thyroiditis (n = 1 (1%)), hyperparathyroidism (n = 1 (1%)) and other (n = 3 (4%)).

Plasma thyroid-stimulating hormone (P-TSH), thyroxine (P-T4), thyroid peroxidase antibody (P-TPOAb), serum thyroid-stimulating hormone receptor antibody (S-TSHRAb) and thyroglobulin antibody (S-TyglAb) levels were available in part of the cases. No serum IgG4 (S-IgG4) were available.

In addition to HT, histopathological diagnoses consisted of malignant neoplasms (n = 32 (39 %), including papillary carcinoma (n = 21), follicular carcinoma (n = 9), medullary carcinoma (n = 1) and anaplastic carcinoma (n = 1)), benign neoplasms (n = 10 (12%), all follicular adenomas), non-neoplastic lesions (n = 15 (18%) including cases of nodular and adenomatous goitre and hyperthyroidism). There were 25 HT cases (31%) without any other accompanying diagnoses. On the other hand, some patients had multiple diagnoses, namely three patients had papillary carcinoma and follicular adenoma and one patient had papillary carcinoma and follicular carcinoma. Follicular epithelial dysplasia (FED) (28) was present in 26 (32%) specimens.

Histomorphological analysis

All representative blocks from each case were histopathologically examined with light microscope. The presence of the following histopathological features was identified from the haematoxylin-and-eosin-stained slides: inflammation, lobulation, stromal and extrathyroidal fibrosis, follicular size and follicular cells abnormalities, obliterative phlebitis and thrombosis. Detailed criteria and grading of assessed histopathological features are presented in (Table 1).

Immunohistochemistry

Immunostaining for CD38 (clone SP149, RTU, Ventana Medical System), IgG (rabbit polyclonal, RTU, Ventana Medical System) and IgG4 (MRQ-44, RTU, Ventana Medical System) was performed with Ventana BenchMark ULTRA (Ventana Medical System) according to the manufacturer's instructions. Tonsil tissue was used as a positive control.

IgG4 scoring

Olympus light microscope model BX51TF (Olympus Europa, Hamburg, Germany) was used to manually calculate IgG4-positive cells using ×400 magnification (high power field, HPF). Areas with the highest density ('hotspot') of IgG4-positive cells were identified using smaller magnification, and the cells of five non-overlapping HPFs were calculated. Mean value of these five HPFs was calculated and used in the analysis. Germinal centres were not included in the hotspots but were calculated separately. The area of one HPF was 0.233 mm^2. IgG4-positive cell count was adjusted by a factor of 0.1476 (0.2330/0.0344 mm^2) to unable the comparison of the results with other studies. IgG4-positive plasma cells to IgG-positive plasma cells ratio was assessed with light microscope by comparing IgG4 immunostained samples to IgG immunostained samples by an experienced pathologist (IK). The following IgG4-positivity threshold criteria were adopted for the analysis: adjusted IgG4-positive plasma cells per HPF > 20 and IgG4- to IgG-positive plasma cell ratio > 30% (20) as the most widely used criteria in the literature (21-23, 29, 30). Of note, the consensus document did not list thyroid gland (9).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics (version 22.0; SPSS, IBM, Armonk, NY, USA).

Table 1. Detailed criteria and grading of histopathological features in Hashimoto thyroiditis cases

Histopathological feature	Detailed description	Grading	Relation to IgG4 positivity
Inflammation	Lymphoplasmacytic infiltration = presence of lymphocytes and plasma cells in the parenchyma	Total percentage (%) of the inflammed parenchyma from the whole thyroid parenchyma	N.S.
	Lymphoplasmacytic penetration into epithelium = presence of lymphocytes and plasma cells in the follicular epithelium	'0' insignificant penetration '1' rare penetration '2' occasional penetration '3' frequent penetration	p = 0.034
	Eosinophils = presence of eosinophils in the parenchyma	'0' insignificant infiltration '1' rare infiltration '2' occasional infiltration	N.S.
	Giant cells = presence of giant cells in the parenchyma	'0' insignificant infiltration '1' rare infiltration '2' occasional infiltration	N.S.
	Neutrophils = presence of neutrophils in the parenchyma	'0' insignificant infiltration '1' rare infiltration '2' occasional infiltration	N.S.
	Total inflammation pattern = localization and distribution of inflammatory cells	Diffuse and/or asymmetric and/or focal distribution pattern	N.S.
Lobulation	The division of the parenchyma into lobules	'0' (insignificant lobulation) '1' (occasional lobulation) '2' (frequent lobulation)	p = 0.057
Fibrosis	Stromal fibrosis = presence of fibrosis in the parenchyma	The total percentage (%) of the fibrous parenchyma out of the whole thyroid parenchyma	N.S.
	Stromal fibrosis = localization and distribution of fibrosis	Diffuse and/or asymmetric and/or focal distribution	N.S.
	Form of stromal fibrosis	Interlobular (%) Interfollicular (%) Scar formation (%)	p = 0.017 p = 0.035 p = 0.016
	Fibrosis outside the thyroid stroma	'0' (insignificant extrathyroidal fibrosis) '1' (mild extrathyroidal fibrosis) '2' (moderate to severe extrathyroidal fibrosis)	p = 0.003
Follicular Size	Microfollicular (diameter < 100 μm), normofollicular (diameter approx. 200–400 μm), and macrofollicular (diameter> 500 μm)	Total number of follicles (100%) in each specimen were divided into three categories: micro-(%), normo-(%), and macro-follicles (%)	Microfollicles > 60% p = 0.003
Follicular Cells Abnormalities	Oncocytic metaplasia	'0' (insignificant metaplasia) '1' (rare metaplasia) '2' (occasional to frequent metaplasia)	p = 0.047
	Squamous metaplasia	'0' (insignificant metaplasia) '1' (rare metaplasia) '2' (occasional to frequent metaplasia)	N.S.
	Basement membrane abnormalities	'0' (absent) '1' (present)	N.S.
	Follicular cell degeneration	'0' (absent) '1' (present)	N.S.
	Follicular cell atrophy	'0' (absent) '1' (present)	p = 0.037
Obliterative Phlebitis	The inflamed vein with closed lumen	'0' (absent) '1' (present)	N.S.
Thrombosis	Formation of a blood clot within a blood vessel	'0' (absent) '1' (present)	N.S.

N.S., non-significant.

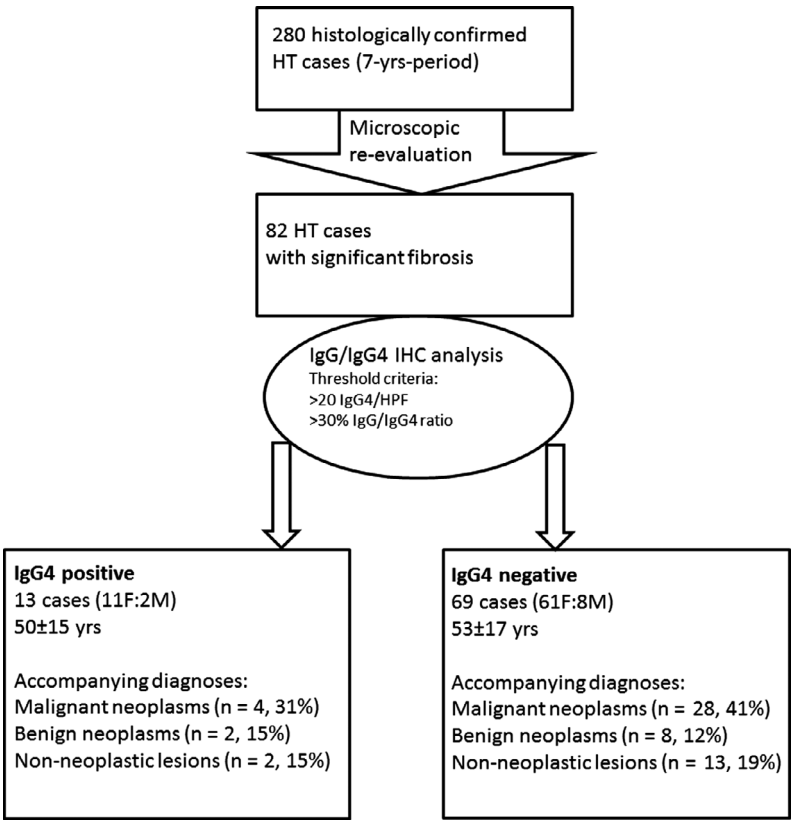

Fig. 1. Flow chart showing subclassification of histologically confirmed cases with HT according to fibrosis and IgG/IgG4 immunohistochemical (IHC) analysis.

The data were analysed using Fisher's exact test (two-tailed), Pearson's chi-square test and Mann–Whitney *U* test. p-values lower than 0.05 were considered statistically significant in all statistical analyses.

Ethical consideration

All procedures were performed in the accordance with the ethical standards of the Ethical Committee of Pirkanmaa Hospital District and with the Helsinki declaration (1975, revised 1983). After the approval by the Ethical Committee, informed consent of each individual was not requested. The use of tissue blocks was approved by the National Supervisory Authority for Welfare and Health (Valvira).

RESULTS

IgG4 scoring

The IgG4-positive HT was defined as cases with both adjusted IgG4-positive plasma cells per HPF > 20 and IgG4/IgG-positive plasma cell ratio > 30% (20, 23) (Figs 1 and 2A–C). IgG4-positive HT group included 13 cases aged 50 ± 15 (range 22–76) years. There were 11 females (85%, aged 52 ± 13 (33–76) years) and 2 males (15%, 35 ± 18 (22–47) years). Adjusted HPF count was 30 ± 5 (23–40) IgG4-positive cells with Median 30 and IQR 4 cells, respectively. The IgG4-positive HT cases formed 15% from fibrotic HT cases and 4.6% from all HT in our cohort. The 69 HT cases that did not fulfil the criteria were aged 53 ± 17 (12–85) years. The group included 61 females (88%, 52 ± 17 (12–85) years) and 8 males (12%, 55 ± 15 (27–72) years). Adjusted HPF count was 6 ± 4 (0–18) IgG4-positive cells with median 6 and IQR 6 cells, respectively.

The IgG4-positive plasma cells were distributed as follows: 26 cases (40%) showed diffuse distribution pattern, 20 cases (31%) showed 'frequent clusters' distribution pattern and the rest showed no pattern or no-IgG4-positivity.

IgG4 and histopathology

Histopathologically, IgG4-positive plasma cells were linked to the presence of oncocytic metaplasia (p = 0.047) and lobulation (p = 0.057). Importantly, significant correlation between adjusted HPF IgG4 counts and various types of fibrosis as interlobular (p = 0.017), interfollicular (p = 0.035) and scar

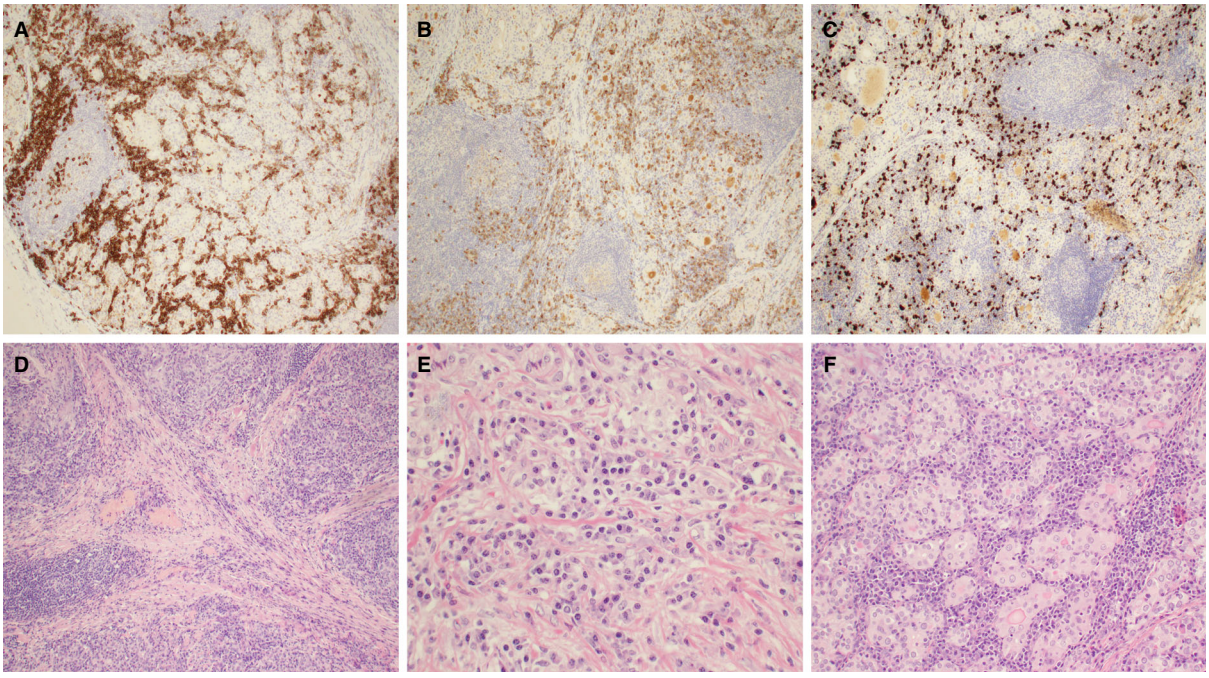

Fig. 2. Immunohistochemical and histopathological characterization of IgG4-positive HT cases. (A) CD38-positive plasma cells in a HT case (CD38, ×100). (B) IgG-positive plasma cells in a HT case (IgG, ×100). (C) IgG4-positive plasma cells in a HT case (IgG4, ×100). (D) Profound fibrosis (graded as 60%, diffuse, predominantly interlobular with interfollicular portion) and inflammatory infiltrate (40%, diffuse) in a HT case (haematoxylin-eosin, ×100). (E) Detailed view of interfollicular fibrosis in a HT case (haematoxylin–eosin, ×400). (F) Oncocytic metaplastic microfollicles (oncocytic metaplasia graded as '2', microfollicles formed 85% of all follicles) surrounded by lymphoplasmacytic inflammation in a HT case (haematoxylin–eosin, ×200).

formation ($p = 0.016$) and fibrosis spread outside the gland ($p = 0.003$) was counted. Lymphocytes/plasma cells penetration into follicular epithelium revealed significant correlation with IgG4 positivity ($p = 0.034$). In addition, IgG4 positivity correlated with the predominance of microfollicles (more than 60%) ($p = 0.003$) and follicular atrophy (0.037) (Fig. 2D–F). In other characteristics, there was no significant difference or trend between histopathology and IgG4-positivity (Table 1).

Interestingly, epithelial degeneration was found in 38 cases (43.7%). Basement membrane abnormalities were observed in 21 cases (24.1%). Only few cases represented giant cells (n = 3, 3.4%) or eosinophils (n = 9, 10.3%). Additionally, phlebitis and thrombosis were observed in only 3 cases (3.4%). Out of 26 cases with FED, only 5 (19%) were in IgG-positive HT group. In IgG4 positive HT cases, three papillary carcinomas and one medullary carcinoma were present (Fig. 1).

Laboratory

No significant differences were found in the laboratory measurements (P-TSH, P-T4, P-TPOAb, TSHRAb, and S-TyglAb levels) between IgG4-positive and IgG4-negative HT cases.

DISCUSSION

We analysed IgG4-positivity in HT in a surgical specimen series in a Finnish population. In a series of 280 HT specimens, 82 (29%) specimens showed fibrosis and out of them 13 cases showed IgG4-positivity using a previously suggested threshold (20-23, 29, 30). The IgG4-positive HT cases formed 15.9% from FVHT cases and 4.6% from all HT in the presented Finnish cohort. In agreement, the only European study revealed 12.6% of IgG4-positive HT with 96% forming FVHT (26). In comparison, Japanese researchers classified 27% of HT as IgG4-positive thyroiditis (21), Chinese authors showed 22.6% (29) and the US study revealed 21% (24). Geographic, genetic and dietary (iodine) variation described in HT (27) can explain also differences in IgG4-positivity and related histopathology in HT in the geographically apart series. Interestingly, Asia origin population predispose to IgG4-RD in the head and neck region with a predilection

to region limited disease (31) as shown also in the thyroid series from Japan and China (20-23, 29, 30).

In the profound histopathological analysis, the presence of lobulation, oncocytic metaplasia and certain type of fibrosis, fibrosis spread outside the gland, lymphocytes/plasma cells epithelial penetration, the predominance of microfollicles and follicular atrophy showed the statistically significant correlation with IgG4-positivity in the present study. Also Desphande et al. notice exaggerated lobulation in their IgG4 positive HT cases (24). Conflicting results were found for the correlation of IgG4 positivity with fibrosis: some studies found statistically significant correlation (21, 24, 29) as in our series, but others did not (25, 30). Microfollicular pattern and follicular atrophy was found to be related to the IgG4 positivity in our study in the agreement with others (22, 24, 25). In our series, 4/13 cases revealed IgG4 positivity also in germinal centres (data not shown) comparable to Kojima study with 2/14 cases (30), but Raess showed extremely lower presence 5/38 (25).

IgG4-RD histopathology is characterized by the presence of individual histopathological features with various percentages with dense lymphoplasmacytic infiltration in almost 100% of cases, fibrosis with a storiform pattern in 74% and obliterative phlebitis and eosinophilic infiltration both in 40% summarized in (32). In the agreement, also published HT cases with IgG4 positivity showed variability in the histopathological characterization. The presence of the histopathological features is also influenced by the stage of the disease or treatment (32). The presence of granulomas and neutrophils generally excludes IgG4-RD (32).

In several elegant papers, Japanese Kakudo led group characterized HT variant as IgG4-RD with specific histopathological, epidemiological, sonographic and laboratory features (20-22). Clinical features as male sex, rapid progress and subclinical hypothyroidism were enlightened in their series (21), but male prevalence was not shown in our and geographically related European (26) and Turkish study (33). Head and neck limited IgG4-RD was suggested to be female or Asian predominant mode (31).

Recently, borderline cases fulfilling either threshold of adjusted IgG4-positive plasma cells per HPF > 20 or IgG4- to IgG-positive plasma cell ratio > 30% were suggested to represent early phase of the disease, where corticosteroid treatment may be beneficial (23). This study was also aimed to search the diagnostic consensus for IgG4-positive HT concluding the presently used criteria as efficient thyroid-specific (23).

The patchy distribution of IgG4 positive cells in the tissue causes the challenge for the analysis (34). Importantly, HPF adjustment is needed to be able to compare the results of various studies (34). In addition, the non-specific presence of IgG4-positive cells in various conditions such as inflammation and lymphoproliferative disorders was reported (10-15, 34) and the presence of both IgG4-positive cells and at least two histopathological features is required (32). IgG4-RD histopathological features are viewed non-specific when individually present, but they possess collectively a strong evidence (32, 35).

The autoimmunity pathogenesis in the IgG4-RD was raised by few authors (6, 31); accordingly, HT is an autoimmune disorder to fulfil this hypothesis.

At least two studies showed the relation of IgG4 positivity in HT to papillary carcinoma either as a risk factor or pathogenetic player (33, 36). Generally, HT is associated with thyroid cancer, particularly thyroid papillary carcinoma (37). On the other hand, decrease of chronic inflammation correlated with more aggressive outcome in thyroid follicular carcinomas (38). The role of FED (28) in the pathogenetic chain waits for more studies in the relation to cancer. In our HT series, 39% cases with malignancy and 12% cases with benign neoplasm were revealed, dominating malignancy being papillary carcinoma. In the IgG4 positive cases, total of 4 malignancies form 30.8% of the cases with three cases of papillary carcinoma and one medullary carcinoma.

Despite the persisting uncertainty whether HT is IgG4-RD, HT with the IgG4-positive plasma cells progress more rapidly into the thyroid tissue destruction and hypothyroidism clinically, so the earlier intervention can be hypothetically warranted in the diagnosed cases (24). The timely diagnosis of IgG4 positivity in HT has additional implication as FVHT may mimic malignancy and tissue and/or serum IgG4 may support inflammatory disease (17, 24), but the higher prevalence of malignancy in HT is acknowledged.

The majority of studies on IgG4 positivity in HT were also retrospective histopathological and immunohistochemical analyses with only sparse clinical and laboratory data, so further larger studies are encouraged. The presented first Nordic series showed comparable histopathological features with previous studies (20-26, 29, 30) and similar epidemiology with another European study (26).

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