Chapter 1

Hashimoto's Thyroiditis

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1. Introduction

1.1. The centennial history of Hashimoto's thyroiditis

One hundred years ago, a 31-year old Japanese surgeon called Hakaru Hashimoto at Kyoto Imperial University published the description of four cases of goiter in the thyroid resection specimens from four women in a German journal Archiv für Klinische Chirurgie in 1912 just before World War I. This paper contained two Latin words in the title (struma lymphomatosa) and five microphotographs. The histological appearance of these goiters characterized by a lymphoplasmocytic infiltrate with diffuse inflammatory alterations of the thyroid parenchyma and fibrosis was very different from the colloid goiters that he was familiar with, as well as those from Grave's disease, infectious thyroiditis (especially related to tuberculosis or syphilis) and the fibrous thyroiditis described by Riedel in 1896. He emphasized similarity with the histological data observed with lacrimal, salivary, lymph node and splenic involvement of Mikulicz's disease (now Sjögren's syndrome). Mickulicz was the teacher of Hayari Miyake, the head of Hashimoto's department.

The four observed cases involved female patients over the age of 40 years who had formed very firm diffuse goiters, to the extent that the diagnoses were suggestive of fibrous thyroid or cancer at that time. But these were isolated, with hardly any severe signs of compression and no adenopathy. The postoperative course of these goiters seemed more complicated than usual. One case was complicated by recurrence, soon followed by spontaneous reduction of the hypertrophy.

Hashimoto decided to continue his training in Göttingen, Germany and then in England. He was forced to return home after the outbreak of World War I. He continued to practice as a general practitioner in rural Midai in 1916 and died in 1934 at the age of 52 years from typhoid contracted from a patient, without achieving the recognition he deserved.

Hashimoto's discovery was not exactly ignored for the next few decades, but recognition of its existence was certainly slow, possibly related in part to the publication of the paper in German. In 1931, Graham and McCullagh used the term ''Hashimoto'' for the first time in the title of an article, strongly arguing that struma lymphomatosa was indeed distinct from Riedel's thyroiditis. The description of lymphocytic thyroiditis was rediscovered in the United States in 1936, and the disease was labeled Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) in medical textbooks. In 1939, the prominent British thyroid surgeon Cecil Joll coined the term ''Hashimoto disease'' and used it in the title of a review he wrote about this condition. Since then, Hashimoto's thyroiditis has gone from being a rarity to one of the most common autoimmune diseases, as well as the most common endocrine disease.

An essential step was the characterization in 1956 by Noel Rose and Ernest Witebsky of experimental thyroiditis created by the injection of thyroid extracts and Freund adjuvant in rabbits, which showed histological aspects similar to those described by Hashimoto. In the same year, Ivan Roitt and Deborah Doniach reported the presence of autoantibodies directed against thyroglobulin in the Lancet. Until then it had seemed inconceivable that an individual would develop antibodies directed against his own body (''horror autotoxicus''). This was the first time that the possibility of autoimmune diseases had been suggested, and Hashimoto's disease established itself as the model of organ-specific autoimmune diseases. It is a good example of a situation in which a brilliant clinician provided the clinical and anatomopathological description of a disease, leaving it to future generations to understand the mechanism and, in the current case, to establish the far-reaching concept of autoimmune diseases, sometimes organ-specific, polyglandular or general.

With regard to history, there is agreement that the hypertrophic forms of lymphocytic thyroiditis, which can progress to atrophy although not inevitable, would be labeled Hashimoto's thyroiditis. In terms of the pathogenic, histologic and biologic perspectives, these forms did not differ greatly from atrophic lymphocytic thyroiditis causing myxoedema, or asymptomatic autoimmune thyroiditis or thyroiditis occurring with nodules or cancer. These aspects are the subject of the article by Orgiazzi. Even before the description of lymphocytic thyroiditis by Hashimoto, the simultaneous occurrence of hypothyroidism with other endocrinopathies had been demonstrated in Germany in 1904 by Erhlich, and in 1908 in France by Claude and Gougerot. In 1980 these conditions of polyglandular failure were divided into four types by Neufeld, and then grouped into two varieties. Childhood-onset type 1 autoimmune polyendocrine syndrome has autosomal recessive transmission linked to a mutation of the AIRE gene, which controls the production of antibodies at the thymic and peripheral levels. This can be differentiated from type 2 (or 2/3), which is much more frequent, starts in adulthood, and is polygenic and multifactorial, the characteristics of which are presented by Kahaly. Whether isolated or occurring with polyendocrinopathies, autoimmune involvement of the adrenal glands alters the quality of life and is life-threatening; it is explained and its care are described in the article by Napier and Pearce. The pathogenic access and assessment of autoimmune involvement in parathyroid and pituitary are still in the early stages, while the immunologic and pathogenic data and management perspectives are better understood in diabetes mellitus, as confirmed in the article by Boitard. The description of the histological changes of Hashi-

moto's thyroiditis, only just a century ago, gained credibility over several decades. Hashimoto's thyroiditis is now considered the most prevalent autoimmune disease.

2. Prevalence over time

Its incidence is about 1 case per 1000 persons per year. The prevalence is 8 cases per 1000 when estimated from a review of published articles, and 46 cases per 1000 when estimated from the biochemical evidence of hypothyroidism and thyroid autoantibodies in subjects participating to the Third National Health and Nutrition Examination Survey. Caturegli(Caturegli, De Remigis et al. 2013) and colleagues have marked the centenary of Hashimoto's seminal paper by reviewing the extensive surgical pathology archives of the Johns Hopkins Hospital for cases of Hashimoto thyroiditis, spanning an extremely long period from 1889 to 2012. The results are fascinating and a fitting way to mark this important anniversary. The study reveals a remarkable change in incidence, with very few cases for the first half of the period, and then a significant increase between 1943 and 1967, a constant incidence up to 1992 and then another significant increase over the last two decades.

Of course this retrospective pathological analysis can take little account of the clinical reasons for thyroid surgery, which will have a fundamental impact on the incidence, but the results are so striking that a rapid increase in the frequency of Hashimoto's thyroiditis in the second half of the 20th century seems an unavoidable conclusion. Another review supported this by reviewing of 1050 Austrians patients who had surgery for benign goiter between 1979 and 2009; there was a significant increase in the incidence of both lymphocytic thyroiditis and Hashimoto's thyroiditis in resection specimens over this time. In addition, a striking rise in Hashimoto's thyroiditis has been reported recently in Italy. Between 1975 and 2005, there was a 10-fold rise in incidence: patients have become relatively younger, are more likely to be male, and have lower autoantibody responses. While some of this change in incidence could be the result of increased thyroid function testing and earlier detection of disease, the overwhelming conclusion is that environmental factors must be responsible. Increased iodine intake is certainly one possible influence: a recent study in China showing increases in subclinical hypothyroidism and autoimmune thyroiditis in an area of more than adequate iodine intake is the latest among many such reports. But not all studies have shown an adverse effect of excess dietary iodine (possibly related to genetic factors and the rate of the increase in iodine intake in a population) and when it does occur, the effect of iodine may be transient. Nor is thyroid autoimmunity alone in this regard; celiac disease, type 1 diabetes, and multiple sclerosis have all increased in incidence over the last three decades. It is likely that aspects of urbanized living, such as higher standards of hygiene, increased prosperity, and increased exposure to environmental toxins, are responsible for this generalized trend, perhaps by altering the balance between T helper cell subtypes.

3. Pathogenesis and etiology

The pathogenesis of Hashimoto's thyroiditis has elicited interest since it was first reported. Dr. Hashimoto himself speculated on possible explanations of what he saw under the microscope, eventually concluding ''at present we cannot say anything definite about the cause''. Initial theories postulated this disease was due to infection, understandably, since infections were quite common and a large focus of clinical investigation, but no clear link with microorganisms was ever found. Other theories considered the Hashimoto goiter a premalignant condition. Some scholars believed the thyroid itself possessed a lymphogenic secretory capability that became hyperactive in these patients. Others viewed the goiter as secondary to constant anxiety and emotional unrest. In 1951, Hellwig proposed the colloidophagy theory, based on rodent studies performed in the late 1920s and his own observations in humans that macrophages exist in the thyroid gland and are capable of ingesting colloid. He postulated that thyroid macrophages that have engulfed colloid degenerate and release colloid, which then attracts lymphocytes into the thyroid. Finally, in the early 1950s, the field of autoimmunity began to take shape; animal models were being developed in which injection of a tissue extract was capable of reproducing a lymphocytic infiltration of that particular organ. This experimental approach was applied to the thyroid when, in 1956, lymphocytic infiltration of the rabbit thyroid was induced by injection of rabbit thyroid extracts. The horror autotoxicus dogma was dismantled and autoimmunity became recognized as an important mechanism of disease. In the ensuing five decades, numerous studies have greatly expanded our understanding of the pathogenesis of Hashimoto's thyroiditis and helped translating research findings into clinical practice. We have known since the mid-1980s that thyroperoxidase is a dominant protein antigen targeted by the patient's immune system in Hashimoto's thyroiditis, and, as a result, antibodies to thyroperoxidase are now considered the most sensitive and specific biomarkers to establish this diagnosis. They also have a predictive value since their presence precedes a clinical diagnosis of Hashimoto's thyroiditis by at least 7 years. We have also known since 1971 that Hashimoto's thyroiditis, like other autoimmune diseases, has a genetic basis. Substantial efforts have been devoted to identify the genes that predispose to Hashimoto's thyroiditis, but results have been less fruitful than expected. Genome-wide association studies and candidate gene approaches have identified a handful of confirmed susceptibility genes (MHC class II region, CTLA-4, PTPN22, and ARID5B), each making, however, only a small contribution to the disease phenotype and through mechanisms that remain to be discovered.

4. Susceptibility genes

4.1. Human leukocyte antigen (HLA) genes

The first gene locus identified in association with the autoimmune thyroid disease was major histocompatibility complex (MHC) region on the chromosome 6p21 which encodes human leukocyte antigens (HLAs). HLA region, which is highly polymorphic, comprises several

immune response genes. HLA molecule, located on antigen presenting cell (APC), binds and presents an antigenic peptide and in this way enables T cell recognition and response to an antigen. Presumably, specific HLA alleles have a higher affinity for autoantigenic thyroidal peptides and are thus likely to contribute to the development of the autoimmune thyroid disease. Nevertheless, in order to initiate the thyroid autoimmunity autoantigen occurrence within thyroid or thyroid draining lymph nodes is needed, being followed by HLA presentation. In HT, aberrant expression of HLA class II molecules on thyrocytes has been demonstrated. Presumably, such thyrocytes may act as APCs capable of presenting the thyroid autoantigens and initiating autoimmune thyroid disease. In Caucasians, associations of different forms of HT with various HLA alleles were reported, including DR3, DR5, DQ7, DQB1*03, DQw7 or DRB1*04-DQB1*0301 haplotype. In Japanese, associations with DRB4*0101, HLA-A2 and DRw53 were demonstrated, while in Chinese patients association with DRw9 was observed (Hawkins, Lam et al. 1987, Honda, Tamai et al. 1989, Badenhoop, Schwarz et al. 1990, Tandon, Zhang et al. 1991, Bogner, Badenhoop et al. 1992, Wan, Kimura et al. 1995, Hunt, Marshall et al. 2001, Petrone, Giorgi et al. 2001, Jacobson, Huber et al. 2008, Zaletel and Gaberscek 2011).

4.2. Cytotoxic t lymphocyte antigen-4 (CTLA-4) gene

CTLA-4 gene, which is the second major immuneregulatory gene related to autoimmune thyroid disease, lies on chromosome 2q33. The expression of CTLA-4 on the surface of T cells induced by the activation of the T-cell receptor results in suppression of T-cell activation. CTLA-4 gene polymorphisms may reduce expression or function of the CTLA-4 antigen and may therefore contribute to the reduced inhibition of T-cell proliferation and subsequently increase susceptibility to autoimmune response. In the past, several polymorphisms of the CTLA-4 gene in HT patients were studied. Among them, the initially reported (AT)n microsatellite CTLA-4 polymorphism in the 3′ untranslated region (UTR) was found to be associated with HT in Caucasian and Japanese patients, but not in Italian population. In the exon 1 located 49A/G single nucleotide polymorphism (SNP), resulting in threonine to alanine substitution, was associated with HT, however, certain other studies have not confirmed this observation. A large meta-analysis, including both published and unpublished data of 866 HT patients, indicated a significant association with 49A/G (summary OR 1.29; 95% CI, 1.11-1.50). Another CTLA-4 polymorphism is 6230A/G SNP which is located at 3′-UTR and designated CT60. Initial observation of the association with HT was not confirmed by later studies, however, the results of the meta-analysis, based on six published and unpublished studies of 839 HT patients, indicated a significant association with CT60 SNP (summary OR 1.64; 95% CI, 1.18-2.28). Nevertheless, the exact mechanism conferring the susceptibility to HT has not been elucidated yet and further studies are needed to determine which CTLA-4 polymorphism is causative.

4.3. Protein tyrosine phosphatase nonreceptor-type 22 (PTPN22) gene

PTPN22 is the most recently identified immuneregulatory gene associated with the autoimmune thyroid disease, which is located on chromosome 1p13. PTPN22, which is predomi-

nantly expressed in lymphocytes, acts as a negative regulator of T-cell activation, much like CTLA-4. 1858C/T SNP of the PTPN22 gene, resulting in arginine to tryptophan substitution at codon 620 (R620W), was demonstrated to be a risk factor for many autoimmune diseases. The mechanism is not clear since the disease predisposing T allele has been demonstrated to enable even more efficient inhibition of T-cell activation. Presumably, weaker T-cell signalling may lead to impaired thymic deletion of autoreactive T cells or an increased PTPN22 function may result in inhibition of regulatory T cells (Tregs), which protect against autoimmunity. An early study in HT patients demonstrated a significant association with 1858C/T SNP (OR 1.77; 95% CI, 1.56-3.97). Afterwards, this observation was neither confirmed in German, Tunisian and Japanese populations nor in Slovenian patients. In a small group of patients with both HT and autoimmune diabetes, T allele was determined in 50% compared with only 14% in healthy controls (OR 6.14; CI, 2.62-14.38), however, in a yet another study estimating the same polymorphism this association was not confirmed. Recently, 5 other PTPN22 SNPs have been tested in Japanese patients, showing no relation with HT, but a novel protective haplotype containing those SNPs has been observed (Ban, Tozaki et al. 2005, Kahles, Ramos-Lopez et al. 2005, Chabchoub, Teixiera et al. 2009, Dultz, Matheis et al. 2009, Ban, Tozaki et al. 2010, Kordonouri, Hartmann et al. 2010, Zaletel and Gaberscek 2011).

4.4. Thyroglobulin gene

Tg is an important thyroid specific antigen, also present in the circulation, which makes it an easy target of the autoimmune response. Gene for Tg is located on the chromosome 8q24 and linkage of this region with HT and autoimmune thyroid disease was first identified by a Japanese and an American whole genome studies. A subsequent fine mapping of this region exposed Tg gene as one of the major thyroid specific susceptibility genes, linked and associated with the autoimmune thyroid disease. Later, different alleles of various microsatellite markers and different SNPs of Tg gene were related to HT, possibly affecting its expression, antigenicity, iodination, or binding to HLA. The association of Tgms2 microsatellite marker in intron 27 with HT was confirmed in Japanese as well as in Caucasian population. Sequencing of human Tg revealed 14 SNPs among which four SNPs, including exon 10-12 SNP cluster and exon 33 SNP, were associated with HT. However, this observation was neither confirmed in a larger data set of the United Kingdom Caucasian patients nor in Chinese population.

4.5. Vitamin D receptor gene

Vitamin D, which acts via vitamin D receptor (VDR), possesses immunomodulatory properties and its deficiency has been implicated in the development of autoimmune diseases. Many immune cells express VDR, dendritic cells in particular, where VDR stimulation has been shown to enhance their tolerogenicity. Tolerogenic dendritic cells promote development of Tregs with suppressive activity and therefore peripheral tolerance. VDR gene is located on the chromosome 12q12 and its polymorphisms have been related to different autoimmune disorders such as type 1 diabetes or Addison's disease. A decade ago, the association between VDR-FokI SNP in exon 2 and HT has been identified which was later confirmed in the observation of Taiwanese Chinese patients. In the Croatian population VDR gene 3′ region

polymorphisms were related to HT, possibly affecting VDR mRNA expression. A significant relation has also been discovered between HT and both promoter and intron 6 gene polymorphisms of CYP27B1 hydroxylase, which is located on chromosome 12q13, catalysing the conversion of 25 hydroxyvitamin D3 to its active form.

4.6. Cytokine genes and other immune-related genes

Lately, several genes encoding different inflammatory cytokines have been studied in HT, some of them also influencing the severity of the disease. Interferon (IFN)-γ, produced by T-helper type 1 (Th1) cells, promotes cell mediated cytotoxicity which underlies thyroid destruction in HT. T allele of the+874A/T IFN-SNP, causing the increased production of IFN-γ, was associated with severity of hypothyroidism in HT patients. Higher frequency of severe hypothyroidism was also observed in patients carrying CC genotype of-590C/T interleukin 4 (IL-4) SNP, leading to a lower production of IL-4, one of the key Th2 cytokines which suppresses cell-mediated autoimmunity. Gene polymorphism of transforming growth factor(TGF)-β, inhibitor of cytokine production, was also associated with HT. T allele of+369T/C SNP, leading to a lower secretion of TGF-β, was more frequent in severe hypothyroidism than in mild hypothyroidism. Similarly, more severe form of HT was associated with-2383C/T SNP of gene for forkhead box P3 (FoxP3), an essential regulatory factor for the Tregs development. Unlike the severity of hypothyroidism, the development of HT itself was associated with C allele of tumor necrosis factor (TNF)--1031T/C SNP. Namely, C-allele carriers present with higher concentration of TNF-which acts as the stimulator of the IFN-production.

5. Risk factors

5.1. Role of female sex and reproduction

5.1.1. Female sex

As indicated by numerous epidemiological studies, females present with positive thyroid autoantibodies (TAbs) up to three times more often than males. The largest NHANES III study has shown that females were positive for TPOAbs and TgAbs in 17% and 15.2%, respectively, while males only in 8.7% and 7.6%, respectively. According to the estimation provided by the study of Danish twins, the genetic contribution to TPOAb and TgAb susceptibility in females was 72% and 75%, respectively, while in males it was only 61% and 39%, respectively. The possible explanation for high female predominance in thyroid autoimmunity might be associated with the X chromosome containing a number of sex and immune-related genes which are of key importance in the preservation of immune tolerance. Increased immunoreactivity might therefore be related to genetic defects of the X chromosome, such as structural abnormalities or monosomy. Accordingly, a higher incidence of thyroid autoimmunity was reported in patients with a higher rate of X chromosome monosomy in peripheral white blood cells or in patients with Turner's syndrome. Another potential mechanism of impaired immunotolerance in females is skewed X-chromosome inactivation (XCI) leading to the escape

of X-linked self-antigens from presentation in thymus with subsequent loss of T-cell tolerance. Skewed XCI was associated with a higher risk of developing autoimmune thyroid diseases. Recently reported frequencies of skewed XCI in HT were 31%, 34.3%, 25.6% and 20%, respectively, which is significantly higher than in healthy controls, where the prevalences were only 8%, 8%, 8.6% and 11.2%, respectively. Furthermore, a study of Danish twins demonstrated a significant association of skewed XCI with TPOAb serum concentrations in dizygotic but not in monozygotic twin pairs, indicating that shared genetic determinants of XCI pattern and TPOAb production are more likely than causal relationship.

5.1.2. Pregnancy and postpartum period

The tolerance of the fetal semi-allograft during pregnancy is enabled by the state of immunosuppression which is a result of hormonal changes and trophoblast expression of key immunomodulatory molecules. The pivotal players in regulation of the immune response are Tregs, which rapidly increase during pregnancy. Consequently, both cell-mediated and humoral immune responses are attenuated with a shift towards humoral immune response, resulting in immune tolerance of the conceptus tissues and suppression of autoimmunity. Accordingly, the decrease of both TPOAb and TgAb concentrations during pregnancy has been reported, reaching the lowest values in the third trimester. Postpartum rapid decrease of Tregs and re-establishment of the immune response to the pre-pregnancy state may lead to the occurrence or aggravation of the autoimmune thyroid disease. The increase of TPOAb concentrations occurred as soon as 6 weeks after delivery, reaching the baseline level at approximately 12 weeks and the maximum level at about 20 weeks after delivery. In up to 50% of females with positive TPOAbs in the early pregnancy, thyroid autoimmunity in the postpartum period exacerbates in the form of postpartum thyroiditis. It may occur within the first year after delivery, usually clinically presented with transient thyrotoxicosis and/or transient hypothyroidism, while in about a third of females permanent hypothyroidism may even develop.

5.1.3. Fetal microchimerism

The term fetal microchimerism is defined by the presence of fetal cells in maternal tissues which are transferred in the maternal circulation during pregnancy. Several years after the delivery, the chimeric male cells can be detected in the maternal peripheral blood as well as in maternal tissues, such as thyroid, lung, skin, or lymph nodes. The fetal immune cells, settled in the maternal thyroid gland, may become activated in the postpartum period when the immunotolerance ceases, representing a possible trigger that may initiate or exaggerate the autoimmune thyroid disease. In HT, fetal microchimeric cells were detected in thyroid in 28% to 83% which means that their occurrence is significantly higher than in the absence of autoimmune thyroid disease. Furthermore, a recent study of twins supported the putative role of microchimerism in triggering thyroid autoimmunity, showing a significantly higher prevalence of TAbs in opposite sex twins compared to monozygotic twins. Additionally, euthyroid females having been pregnant presented significantly more often with positive TPOAb compared to females with no history of being pregnant. However, the relation between parity and autoimmune thyroid disease was not confirmed by large population-based studies, advocating

against the essential contribution of fetal microchimerism to the pathogenesis of autoimmune thyroid disease.

6. Environmental triggers

6.1. Iodine intake

Excessive iodine intake is well-established environmental factor for triggering thyroid autoimmunity. Several large population-based studies demonstrated higher prevalence of TAbs in the areas with higher iodine supply since the estimated prevalence was approximately 13% in iodine deficiency, 18% in circumstances of sufficient iodine intake and about 25% in areas with excessive iodine intake. Moreover, up to four-fold increase in prevalence of TAbs was demonstrated after the exposure to higher iodine intake due to the improvement of iodine prophylaxis in previously iodine deficient areas. According to the intervention study, deliberate exposure to 500 μg of iodine provoked thyroid autoimmunity in 20% of previously healthy individuals. Valuable evidence was also provided by using experimental animal models of autoimmune thyroiditis, where the prevalence and severity of thyroid autoimmunity significantly increased when the dietary iodine was added (Kahaly, Dienes et al. 1998, Rose, Bonita et al. 2002, Fountoulakis, Philippou et al. 2007, Golkowski, Buziak-Bereza et al. 2007, Heydarian, Ordookhani et al. 2007).

Several putative mechanisms by which iodine may promote thyroid autoimmunity have been proposed. Firstly, iodine exposure leads to higher iodination of Tg and thus increases its immunogenicity by creating novel iodinecontaining epitopes or exposing cryptic epitopes. This may facilitate presentation by APC and enhance the binding affinity of the T-cell receptor which may lead to specific T cell activation. Secondly, iodine exposure has been shown to increase the level of reactive oxygen species in the thyrocyte which is generated during TPO oxidation of excessive amounts of iodine. They enhance the expression of the intracellular adhesion molecule-1 (ICAM-1) on the thyroid follicular cells which could attract the immunocompetent cells into the thyroid gland. Thirdly, iodine toxicity to thyrocytes has been reported, since highly reactive oxygen species may bind to membrane lipids and proteins, causing thyrocyte damage and release of autoantigens. Fourthly, iodine excess has been shown to promote follicular cell apoptosis by inducing an abnormal expression of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) and its death receptor (DR)-5 in thyroid. Fifthly, in vitro evidence also suggests an enhancing influence of iodine on the cells of the immune system, including augmented maturation of dendritic cells, increased number of T cells and stimulated B-cell immunoglobulin production.

6.2. Drugs

Furthermore, certain drugs were reported to trigger or exacerbate thyroid autoimmunity in susceptible individuals (Barbesino 2010, Hamnvik, Larsen et al. 2011). Interferon-α (IFN-α) is extensively used to treat chronic hepatitis and is frequently associated with thyroid autoimmunity since TAbs were observed in up to 40% and clinical disease in 5-10% of patients treated

with IFN-α. Presumably, IFN-α has both thyroid toxic effects with consequent autoantigen presentation and immune effects, such as switching to Th1 immune response, suppression of Treg function, activation of immune cells, stimulation of cytokine release and expression of MHC class I on thyroid cells. Similarly, IL-2 treatment, used for melanoma and renal carcinoma, seems to act via immune and toxic mechanisms, leading to both TAb positivity and hypothyroidism.

In patients with known autoimmune thyroid disease lithium may increase the risk of hypothyroidism. According to some studies, treatment with lithium has also been shown to increase TAb titres and the prevalence of thyroid autoimmunity. Among putative mechanisms direct toxicity of lithium on thyroid or toxicity of increased intrathyroidal iodine resulting from lithium treatment were discussed. Similarly, amiodarone alone as well as its high iodine content may act cytotoxically which may lead to thyroid autoantigen presentation and provoke thyroid autoimmunity.

More recently, some small molecule tyrosine kinase inhibitors (TKIs) used for the treatment of metastatic renal cell carcinoma (Muriel, Esteban et al. 2010, Kollmannsberger, Bjarnason et al. 2011, Eisen, Sternberg et al. 2012, Mendez-Vidal, Martinez Ortega et al. 2012, Bianchi, Rossi et al. 2013), gastrointestinal stromal tumours (Joensuu, Trent et al. 2011), thyroid carcinoma and pancreatic neuroendocrine tumours have been shown to cause hypothyroidism related symptoms to a variable extent, which can reduce a patient's quality of life (Torino, Corsello et al. 2009, Zygulska, Krzemieniecki et al. 2012). Sunitinib and sorafenib are multitargeted TKIs that have been demonstrated to induce hypothyroidism and thyroid dysfunction. The reported incidence of sunitinib-induced hypothyroidism is 53-85% and 36-46% in retrospective or prospective studies, respectively, and 18% in patients treated with sorafenib (Torino, Corsello et al. 2009). Mechanisms of hypothyroidism induced by TKIs include drug-induced atrophy of the thyroid through inhibition of its vascularization, drug-induced thyroiditis, reduced synthesis of thyroid hormones, progressive depletion of the thyroid's functional reserve and inhibition of the thyroidal iodine uptake (Torino, Corsello et al. 2009). Makita *et al* (Makita and Iiri 2013) and Bianchi *et al* (Bianchi, Rossi et al. 2013) thought that sunitinib may exert these effects via multiple receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) and the platelet-derived growth factor receptor (PDGFR). In patients treated with sunitinib or sorafenib, routine thyroid function testing at baseline and measurement of TSH on day 1 at the start of every new treatment cycle is recommended. Levothyroxine is the standard treatment for overt hypothyroidism and is recommended in some patients with subclinical hypothyroidism; overt or subclinical hypothyroidism *per se* does not justify the withdrawal of TKI therapy. Thyroid function test should be included in routine toxicity assessment of TKIs under clinical evaluation (Torino, Corsello et al. 2009, Hamnvik, Larsen et al. 2011, Eisen, Sternberg et al. 2012); however, the clinical relevance of early diagnosis of hypothyroidism in patients with TKIs is still controversial.

6.3. Infections

Not only the IFN-α treatment but also hepatitis C infection itself has been reportedly associated with thyroid autoimmunity and hypothyroidism. Among possible mechanisms, the molecular

mimicry between viral and selfantigens has been suggested, whereas the release of proinflammatory mediators caused by viral infection may lead to activation of autoreactive T-cells. Besides, in HT several other putative triggering viruses have been implicated such as parvovirus, rubella, herpes simplex virus, Epstein Barr virus, and human T-lymphotropic virus type 1. A recent study of sera in pregnant women has also indicated an association between a prior infection with Toxoplasma gondii and an increase of TPOAbs. Nevertheless, the evidences are scarce and further studies are required in order to confirm the role of infections as causative agents.

6.4. Chemicals

The exposure to environmental toxicants such as polyaromatic hydrocarbons or polyhalogenated biphenyls, both commonly used in a variety of industrial applications, has been shown to provoke thyroid autoimmunity not only in experimental animals but also in humans. Recently, a significantly higher prevalence of HT and TAb (9.3% and 17.6%, respectively) has been demonstrated in residents living in the area of petrochemical complex of Sao Paolo compared to the control area (3.9% and 10.3%, respectively). In Slovakia, the exposure to polychlorinated biphenyls was associated with TAb and hypothyroidism. Although there is strong evidence attesting the contribution of chemicals to thyroid autoimmunity, the exact mechanisms of their action are yet to be established (Langer, Tajtakova et al. 2007, de Freitas, Grimaldi Campos et al. 2010).

7. Hashimoto's thyroiditis and papillary thyroid carcinoma

There has long been a controversy in the literature about a possible link between HT and PTC. Conflicting reports continue to emerge. Some suggest a positive correlation between the two, and even a cause-and-effect relationship, whereby the activated inflammatory response present in HT creates a favorable setting for malignant transformation. The inflammatory response may cause DNA damage through formation of reactive oxygen species, resulting in mutations that eventually lead to the development of PTC. Nevertheless, it remains unclear whether: (1) HT predisposes patients to develop PTC, (2) HT is an incidental finding with concurrent PTC, or (3)HT is a part of the host tumor response system. A meta-analysis done by Jankovic (McLeod, Watters et al. 2012, Jankovic, Le et al. 2013) revealed significant differences in the prevalence and the risk ratio of PTC in HT specimens obtained via FNAB vs thyroidectomy.

In population based studies where the specimens were obtained from FNAB, the average prevalence of PTC in patients with HT was 1.20%, with an average risk ratio of 0.69. Conversely, in studies from archival thyroidectomy specimens, the average prevalence and risk ratio were as high as 27.56% and 1.59, respectively. This variability could be a result of different methods of obtaining specimens and heterogeneity in the population under investigation in terms of ethnic, geographic, and gender differences.

The prevalence and the risk ratio of PTC in patients with HT compared to those without HT are significantly higher in studies of thyroidectomy specimens, compared to studies of patients undergoing FNAB. In studies that mentioned the indications, thyroidectomy was reserved for patients not responding to thyroid suppression therapy, those with symptoms of compression, worrisome or inconclusive FNA cytology, and historic or physical findings warranting further workup and treatment (e.g., irradiation, nerve paralysis, pain, or cervical lymph node enlargement). It should be noted that the vast majority of patients with HT do not require surgery. Hence, the patients who require thyroidectomy are already at higher risk for malignancy compared to the general population with HT.

There have been a number of proposed hypotheses to explain the linkage between the two diseases. From a histological perspective, Tamimi (Tamimi 2002) assessed the prevalence and severity of thyroiditis among three types of surgically resected thyroid tumors and found a significantly higher rate of lymphocytic infiltrate in patients with PTC. However, PTC with concurrent HT is associated with female gender, young age, less aggressive disease such as small tumor size, less frequent capsular invasion and nodal metastasis, and better prognosis. Furthermore, these patients are also less likely to develop recurrence and have a higher survival rate In the study by Eisenberg et al(Eisenberg and Hensley 1989), none of the patients with a thyroid carcinoma and HT developed relapse or metastases after 74 months of follow-up. Kebebew (Kebebew, Treseler et al. 2001) demonstrated that CLT correlates with improved survival in patients with PTC but is not an independent prognostic factor. Boi et al investigated the relationship between thyroid autoimmunity and thyroid cancer in a series of FNAB of unselected and consecutive thyroid nodules. This study revealed that the positive predictive values for thyroid carcinoma in antithyroid antibody-positive and –negative nodules are not statistically significant for class III (indeterminate risk) and class IV (suspected malignancy) cytology. It should be noted that it is important to distinguish between diffuse vs focal lymphocytic infiltration around the tumor. In the studies that described the histological findings, HT was defined as diffuse lymphocytic infiltration, rather than peritumoral lymphocytic infiltration alone. The significance of this is that HT does not represent a reaction to tumor alone but is an independent chronic process. In chronic inflammation, there are reactive alterations of stroma brought on by injury from chemokines, cytokines, and growth factors that cause damage to stromal cells. This in turn may cause malignant transformation in epithelial cells, thereby resulting in tumor development. In contrast, the lymphocytic infiltrate of HT may be an immunological response with a cancer-retarding effect, contributing to a favorable outcome of PTC compared to other thyroid cancers. Moreover, the relatively high prevalence of PTC in autopsy series may represent host immune control. Interestingly, lymphocytic infiltration within or surrounding the tumor was found to correlate with the existence of CLT. This may explain the "protective" effect of CLT in PTC.

Another hypothesis for the causal relationship between HT and PTC is that elevated levels of TSH found in hypothyroid patients with HT stimulate follicular epithelial proliferation, thereby promoting the development of papillary carcinoma (Jankovic, Le et al. 2013). McLeod *et al* (McLeod, Watters et al. 2012) conducted a systemic review that included 5786 thyroid cancer cases in 43 032 subjects and found that serum TSH confers a greater likelihood of

development of thyroid cancer (odds ratio 1.87–2.83, depending on the level of TSH). A subset of studies that was adjusted for autoimmune thyroiditis did not find this relationship between TSH and heightened odds ratio for thyroid cancer. Conversely, several authors identified a few biomolecular markers, including RET/PTC rearrangements, p63 protein, and loss of heterozygosity of hOGG1, that are potentially involved in neoplastic transformation from HT to PTC. So far, no causal genetic linkage has been confirmed.

In conclusion, the existing data provide inconsistent evidence favoring a causal relationship between HT and PTC. Population-based studies using FNAC show no significant increase of PTC in patients with HT, whereas surgical series using thyroidectomy show a heightened risk for coexistent PTC, possibly related to selection bias. Prospective studies involving a large number of subjects and long-term follow-up are needed to further elucidate the relationship. Several studies also suggest that HT appears to confer a better prognosis in patients with PTC, but more research is necessary to further investigate this. At the present time, there is no valid established criterion to identify those patients with HT at a higher risk of developing PTC. Careful observation and follow-up of HT patients is recommended, especially those with nodular variants.

8. Laboratory tests

Elevated anti-TPO or anti-Tg antibody titers are the most specific laboratory findings to establish the diagnosis of autoimmune thyroid disease (AITD) or HT, typically making biopsy unnecessary. The 24-hours thyroid radioactive iodine-123 or-131 (^{123}I or ^{131}I) uptake (RIU) is also helpful to distinguish Hashitoxicosis from Graves' disease (GD); the RIU is low in patients with Hashitoxicosis, whereas it is elevated in those with GD. ^{123}I is preferred than ^{131}I because it has a shorter half-life (13 hours for ^{123}I, 8 days for ^{131}I) allowing quicker dissipation of background radiation. Since radioactive iodine is secreted in breast milk, and ^{123}I has a short half-life, it is recommended for diagnostic thyroid studies in nursing mothers. Breast milk must be pumped and discarded for 2 days after the intake of ^{123}I either used for thyroid uptake or for thyroid scanning.

Scintigraphy reveals in-homogeneous activity throughout the gland in 50% and a pattern suggestive of either hot or cold nodules or a combination of both in 30% of patients. Twenty percent of patient with HT have normal findings at the scintigraphic thyroid imaging.

9. Clinical pictures

Clinical manifestations of HT are variable and commonly include diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism which shows a combination of elevated serum TSH concentrations and normal free T4 and T3 concentrations and permanent hypothyroidism. Not often, HT causes acute destruction of thyroid tissue and release in blood of stored thyroid hormones, causing transient thyrotoxicosis. This condition has been termed "Hashi-

toxicosis" or "painless sporadic thyroiditis", or "painless postpartum thyroiditis" when occurs in women after delivery. In Hashitoxicosis serum TSH is suppressed, and total and free T3 and T4 are elevated. Also, serum T4 is proportionally higher than T3, reflecting the ratio of stored hormones in the thyroid gland, whereas in GD and in toxic nodular goiter, T3 is preferentially elevated. Rarely, a hypofunctioning gland in HT may become hyperfunctioning with the onset of coexistent GD. In patients with GD, HT is usually present concurrently.

10. Treatment

If overt hypothyroidism is present, the treatment of choice for HT is the administration of L-thyroxine (L-T4) in the usual replacement doses. We also use L-T4 to treat patients with HT subclinical hypothyroidism and high serum thyroid antibody concentrations, because in these cases a progression to overt hypothyroidism is common and hyperlipidemia and atherosclerotic heart disease may develop. L-T4 may mildly and indirectly suppress serum concentrations of autoantibodies due to decreased stimulation of thyroid tissue by TSH and causing reduction of antigenic production. The goal of treatment is to restore clinically and biochemically an euthyroid state. For that, free T4 levels must be within the reference range and TSH at the lower half of the reference range. The usual dose of L-T4 is 1.6-1.8 μg/kg per day and is patient dependent. Elderly patients usually require a smaller dose of L-T4, sometimes less than 1μg/kg per day. The initial dose and the optimal time needed to establish the full replacement dose as above should be individualised relative to age, weight and cardiac status.

In HT patients with a large goiter and normal or elevated serum TSH, we think, L-T4 may be given in doses sufficient to suppress serum TSH in an effort to shrink the thyroid theoretically, although randomized studies are needed to verify the long term safety of this method concerning the potential cardiovascular and skeletal side effects. Suppressive doses of L-T4 tend to shrink the goiter by average of 30% over 6 months. If the goiter does not regress, the L-T4 doses are lowered. Goiters that are hard and fibrotic do not respond to L-T4 treatment. If the thyroid gland is only minimally enlarged, the patient is euthyroid and TSH levels are normal, the patient should remain under medical supervision, since hypothyroidism may often develop years later. Also, patients should be informed about the importance of compliance with replacement treatment and instructed to report any symptoms suggesting hyperthyroidism that could be due to an overdosage of L-T4. The intake of L-T4 should be apart by at least 4 hours from other drugs like calcium carbonate, ferrous sulfate, cholestyramine, sucralfate, iron-containing multivitamins, antacids containing aluminum hydroxide, phenytoin sodium, carbamazepine and amiodarone HCL, all of which impair the absorption/metabolism of L-T4.

Selenium (Se) supplementation in patients with AITD, including HT, seems to modify the inflammatory and immune responses, probably by enhancing plasma glutathione peroxidase (GPX) and thioredoxin reductase (TR) activity and by decreasing toxic concentrations of hydrogen peroxide (H_2O_2) and lipid hydroperoxides, resulting from thyroid hormone synthesis. When Se intake is adequate the intracellular GPX and TR systems protect the

thyrocyte from these peroxides, considering that oxidative stress induces TR1 and GPX. The current recommended dietary intake of selenium in humans to achieve the maximal activity of GPX in plasma or in erythrocytes is between 55 and 75μg per day. It must be considered that organic forms of Se such as Se-methionine and yeast-bound Se, have a much lower toxicity and a much higher effectiveness and safety than inorganic Se like sodium selenate. Several studies have revealed a significant reduction of anti-TPO concentrations in patients with AITD treated with 200 μg Se per day for three, six, or nine months (Gartner, Gasnier et al. 2002, Duntas, Mantzou et al. 2003, Gartner and Gasnier 2003, Turker, Kumanlioglu et al. 2006, Mazokopakis and Chatzipavlidou 2007). Duntas et al. found an overall decrease of 46% of AITD at 3 months ($P<0.0001$) and of 55.5% at 6 months ($P<0.05$) of treatment with L-selenomethionine plus L-T4. Others found a decrease of 26.2% at 3 months ($P<0.001$) and an additional 23.7% at 6 months ($P<0.01$) after L-Se-methionine treatment. A significant decrease in the mean serum anti-TPO levels was also noted after the daily intake of 200 μg sodium selenite for 3 months. This decrease amounted to 36.4% in the selenium-taking group of patients versus 12% in the control group ($P=0.013$) (Gartner, Gasnier et al. 2002). A recent study in 80 Greek women with HT showed a significant reduction of serum anti-TPO levels during the first 6 months of L-Se-methionine treatment ($P<0.0001$). Anti-TPO decreased by 5.6% and by 9.9% after 3 and 6 months of L-Se-methionine treatment, respectively. The extension of L-Se-methionine supplementation for 6 more months resulted in an additional 8% decrease, while cessation of treatment resulted to a 4.8% increase, in the anti-TPO concentrations.

A systematic review and meta-analysis done by Toulis (Toulis, Anastasilakis et al. 2010) provided evidence that selenomethionine at a dose of 200 mg once per day is effective in reducing TPOAb titers in patients with HT after a 3-month period, compared with placebo. In absolute numbers, this reduction equals ~300 IU/mL. Efficacy of Se supplementation for >3 months could not be supported, because of lack of evidence from randomized, placebo controlled trials. Patients assigned to Se supplementation had also a threefold higher chance of reporting an improvement in well-being and/or mood, compared with controls. No serious adverse effects were recorded after Se supplementation, with the exception of a limited number of gastric discomfort complaints associated with selenomethionine use. In general, there are no data demonstrating that Se treatment had any impact on the natural course of the disease.

Further controlled and extensive studies are needed to clarify the exact mechanisms by which Se exerts effects on anti-TPO production, and investigate the long-term clinical effects of Se treatment.

In a study involving 21 patients with HT and subclinical hypothyroidism, simvastatin in a daily dose of 20 mg orally for a period of eight weeks improved thyroid function inducing an increase in serum free T3 and free T4 levels and a decrease in TSH levels. Decreases in anti-TPO and anti-Tg antibodies were not statistically significant, possibly by stimulating apoptosis of certain types of lymphocytes. Further controlled and extensive studies are needed to investigate the effectiveness of statins treatment on the course of HT.

Patients with Hashitoxicosis may have only mild thyrotoxicosis and may not require treatment. Antithyroid drug treatment with thiourea drugs is contraindicated, because there is no excess of thyroid hormone production. Patients who have more symptoms should have a 24-

hours thyroid RIU test and a radioiodine scan to determine whether GD may be present and may be treated with beta-blockers. In symptomatically thyrotoxic patients with low thyroid ^{123}I uptake test, propranolol treatment is continued and sodium ipodate or iopanoic acid may also be given in doses of 500 mg daily orally, until the patient is euthyroid. Sodium ipodate and iopanoic acid are known iodinated contrast oral cholecystographic agents that inhibit peripheral 5'-monodeiodination of thyroxine, thereby blocking its conversion to active T_3. Patients having low thyroid RIU do not respond to thiourea medication.

Patients with HT and a large goiter with pressure symptoms such as dysphagia, voice hoarseness, stridor and respiratory distress, may require surgical care. Also, in HT the presence of a malignant nodule or of a thyroid lymphoma diagnosed by histology after a fine-needle aspiration is an absolute indication for thyroidectomy.

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