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Review Article

Hashimot's Thyroditis: Immunopathogensis, Antibody-Associated and Risk of Malignancy

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Abstract: Hashimoto's thyroiditis (HT) is considered as one of the most common immunological disorders influencing the thyroid gland. This disorder affect mostly the middle aged people especially the female inspite that there is no age group exclusion. It is a common cause of hypothyroidism. It was clearly that HT is correlated with thyroid cancers especially papillary thyroid carcinoma and lymphoma. In this article we tried to focus the main points of immunopathogenesis, differential diagnosis and cancer association.

Keywords: Hashimoto's Thyroditis, Autoimmune, Chronic Inflammation.

INTRODUCTION

Hashimoto's thyroiditis(HT) is an autoimmune disorder(also known as autoimmune thyroiditis or lymphocytic thyroditis) that affects the thyroid gland, leading to lymphocytic inflammation with subsequent gradual destruction of thyroid tissue and enlargement of the thyroid gland [1, 2]. It is the most common cause of hypothyroidism in areas with sufficient iodide area in the world. It is accompanied by elevated serum autoantibodies [3]. The disease is firstly discovered by Hakaru Hashimoto. The global incidence of HT is variable and ranges from 0.5 to 1.5 cases per 1000 individuals annually, mostly in female between the age of 30-50 year but can be seen in all ages [4, 5]. The prevalence is 20-30% and accounts for 79.1% of cases of thyroiditis. It is five to six times more in female than male [6, 7].

Regarding the causes and risk Factors, HT is thought to result from a combination of genetic and environmental factors. Genetic predisposition plays a role, as the condition tends to run in families. Certain environmental triggers, such as excessive iodine intake, exposure to radiation, or viral infections, may also contribute to the development of Hashimoto's thyroiditis [8, 9].

The pathophysiology considers HT as an autoimmune disease i.e. the immune system mistakenly identifies the thyroid gland as foreign and begins to produce antibodies against it. These antibodies, including thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), attack and damage the thyroid tissue. This chronic inflammation impairs the thyroid's ability to produce hormones adequately [10, 11].

The symptoms of Hashimoto's thyroiditis can vary widely and may develop slowly over time. The local effect is due to the compression of the gland on the surrounding organs so can produce dysphonia or dysphagia. The systemic effect is due the hypothyroidism and include fatigue, weight gain, sensitivity to cold, constipation, dry skin, hair loss, muscle weakness, depression, and memory problems. Some individuals may also experience goiter [12]. At the primary stage where there is destruction of thyroid follicles, a stage of temporary hyperthyroidism appears but it will subside gradually [13].

GENETIC ABNORMALITIES

Thyroglobulin gene (*TG*) variant was discovered in families with HT. This variant results from splicing site variant of the *TG*. It is already known that polymorphism accompanies the development of the disease, probably due to it's effect on thyroglobulin

release with a rise of inflammatory response [14]. Another mode of inheritance is the hypoinsufficiency of A2 gene(which encodes tumor necrosis factor alpha).This disturbs the TH17 function with a subsequent inflammatory and autoimmune reaction [15]. Other gene abnormalities include major histocompatibility complex (HLA class I and class II), Immunoregulatory genes (like *CTLA4, CD40*) and Genes associated with thyroid peroxidase antibody synthesis (e.g. *TPO, BACH2*) [16].

IMMUNOPATHOGENESIS OF HASHIMOTOS THYRODITIS

The interplay of genetic disorders and environmental factor is considered as the cornerstone in the pathogenesis of Hashimoto's thyroiditis which is considered as an autoimmune disease that is accompanied by infiltration of CD4 cells, macrophages and plasma cells which produce autoantibodies anti thryroid peroxidase(TPO) and thyrohglobulin(Tg) [17].

First there is activation of the antigen presenting cells (APC) which present allo-and auto antigen to naïve CD4 leading to it's differentiation into Th1, Th2Th17, Th22 or Treg. (Th1) cells, play a significant role in the immune response in Hashimoto's thyroiditis. They are activated and release pro-inflammatory cytokines, such as interferon-gamma (IFN- gamma), interleukin-2 (IL-2), and interleukin-17 (IL-17), which contribute to futher differentiation of naïve CD4 into Th1.Cytotoxic T lymphocytes will be activated by the Th-1producing cytokines; IL-2,gamma interferon and TGF-β [18].

Production of Autoantibodies(humoral-mechanism).: B cells in the thyroid gland and lymphoid tissue surrounding it produce autoantibodies, specifically TPOAb and TgAb. B-cell is activated by cytokines released from Th2. These autoantibodies bind to TPO and Tg antigens on the thyroid cells, leading to antibody-dependent cell-mediated cytotoxicity and further destruction of thyroid tissue [17, 19].

Regulatory T Cells: Regulatory T cells (Tregs) play a crucial role in maintaining immune tolerance and preventing excessive immune response. In Hashimoto's thyroiditis, there is evidence of reduced Treg function, which may contribute to the breakdown of immune tolerance and the development of the autoimmune response against the thyroid gland [20].

Finally there is increased thyrocyte-apoptosis due to several mechanisms including Th-1 induction and perforin and Fas ligands produced by CD8-Tcell which are considered as apoptotic factors [21].

HISTOPATHOLOGICAL CHANGES IN HASHIMOTO'S THYRODITIS

The Histopathological examination is crucial to diagnose HT and to differentiate it from other conditions. Lymphocytic Infiltration: The hallmark feature of Hashimoto's thyroiditis is the presence of diffuse lymphocytic infiltration in the thyroid gland. Lymphocytes, particularly T-lymphocytes, infiltrate the thyroid tissue, forming aggregates known as lymphoid follicles with prominence of germinal centers. In HT, the Hurthle cells become enlarged and show increased eosinophilia. Over time, chronic inflammation in Hashimoto's thyroiditis can lead to the deposition of fibrous tissue in the thyroid gland. This fibrosis can disrupt the normal architecture of the thyroid and contribute to the development of a goiter, an enlarged thyroid gland. Epithelial Cell changes can include atrophy, hypertrophy and metaplasia. The lymphocytic infiltration and fibrosis can disrupt the normal arrangement of thyroid follicles. This disruption can lead to the destruction of follicular cells and impair the synthesis and release of thyroid hormones. It's important to note that the histopathological changes in Hashimoto's thyroiditis can vary among individuals and may change at different stages of the disease [22].

ASSOCIATION OF HASHIMOT'S THYRODITIS WITH OTHER AUTOIMMUNE DISEASES

The existence of HT with other specific and systemic organ autoimmune disease was clarified in many articels. The rise of autoantibody titer related to HT was detected in patients with immune disease like autoimmune gastritis, celiac disease, vitiligo, systemic sclerosis, diabetes , Sjogren syndrome rheumatoid arthritis and systemic lupus erythematosus. Graves disease, the other immune-related thyroid disease showed common immunpathogenesis with HT. This focuses the importance of routine and regular checking of thyroid function in patients suffering from auto-immune diseases [23-25].

ROLE OF HASHIMOT'S THYRODITIS IN THYROID CANCER DEVELOPMENT

The association of HT, a chronic autoimmune thyroditis with cancer was demonstrated both in thyroid gland and other organs like gastric cancer since the relation of Autoimmune thyroiditis with the autoimmne gastritis and pernicious anemia and with its' subsequent risk of gastric adenocarcinoma and stomach neuroendocrine tumors [26, 27]. The association of the chronic inflammation was firstly pointed out by Rudolf Virchow in 1893.This fact was later documented in several organ tumors [28]. The relation of HT and the thyroid papillary carcinoma (PTC) is still a controversial issue. The state of hypothyroidism and the consequent increased level of thyroid stimulating hormone(TSH) associated of HT, chronic inflammatory mediators released and associated mutation may mark the etiology of the tumor development in thyroid gland [29, 30]. The chronic inflammation may participates in carcinogenesis by producing mytogenic, antiapoptotic, proangiogenic and lymphangiogenic factors [31].

Paolo De Riol assumed that the relation of HT and increased risk of PTC is undefined [32]. Other

reports insisted that there is indeterminate correlation between HT and PTC [33].

The reported cases of associated with HT ranges from 0.8-38%. The HT disease may affect the prognosis of the proposed PTC. The papillary thyroid carcinoma accompanying HT was found to be smaller size, more multifocal , earlier presentation and less lymph node metastasis than malignant cases not associated with HT [34, 35].

Primary thyroid lymphoma (PTL), a rare thyroid cancer accounts for only 1-5% of all thyroid malignancies. The prevalence of HT in patients with PTL reaches up to 80%. It was found that HT rises the possibility of PTL 40-80 folds. However it is not clear whether HT is a necessary step to develop the lymphoma [36, 37].

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