Review article: history of medicine

Dr Hashimoto and the discovery of autoimmune hypothyroidism

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Abstract. Hashimoto's disease also known as Hashimoto's thyroiditis (HT), is one of the most common autoimmune diseases involving the thyroid gland. HT that it is an organ-specific autoimmune disorder characterized by immune cell infiltration into thyroid tissue and thyroid-specific autoantibodies, causing thyroid gland destruction and, eventually, hypothyroidism which is the common clinical manifestation. The discovery of HT was a significant step in the history of medicine and paved the way toward the discovery of autoimmunity and endocrine disorders. HT was discovered by Dr Hakaru Hashimoto over 100 years ago. Surprisingly, it took several decades to be recognised as separate disease and acknowledged as a discovery of Dr Hashimoto. Herein, we summarize what is known of Dr Hashimoto biography and his discovery in order to shine a light on one of the most important discoveries linked to the thyroid disease and autoimmune disorders as well.

Key words: Hashimoto's disease, autoimmune thyroiditis, hypothyroidism, lymphocyte

Introduction

Autoimmune Thyroid Disorders (AITD), including Hashimoto's disease and Graves' disease, represent 30% of all autoimmune diseases (1). Hashimoto's disease, also known as Hashimoto's thyroiditis (HT), autoimmune thyroiditis or chronic lymphocytic thyroiditis (CAT) was originally termed "struma lymphomatosa" by Dr Hakaru Hashimoto, over 100 years ago. Despite the pathogenesis of HT has not been fully clarified, it is acquired HT that it is an organ-specific autoimmune disorder characterized by thyroid immune cell infiltration and thyroid-specific autoantibodies, causing thyroid gland destruction and, eventually, hypothyroidism. The most frequent forms of HT are the goitrous and atrophic forms (2, 3). HT microscopic picture consists of thyroid infiltration of B and T cells and innate immune cells (dendritic cells, macrophages and natural killer cells). Biochemically, HT is characterized by elevated levels of antibodies directed to thyroid peroxidase (TPOAb). In the advanced stages the disease present elevated levels of antibodies directed to thyroglobulin (TgAb) and, in most cases, high thyrotropin (TSH) levels and low circulating thyroid hormone levels.

Biography of Dr Hakaru Hashimoto

Dr Hakaru Hashimoto was born in 1881, in the Japanese village of Iga-cho, Ayama-gun, to a family who had been practicing medicine for four generations. In 1903 he was enrolled in Fukuoka Medical College, which was newly established as a branch of

the Faculty of Medicine of Kyoto Imperial University. He graduated in 1907 (4). Following graduation, he enrolled the First Surgical Bureau where, under the supervision of Professor Hayari Miyake (1867–1945), a specialist in visceral and cancer surgery, he studied medicine. Prof. Miyake had a great interest in thyroid diseases, probably influenced by his professors in Germany including Prof Mikulicz, and later by Theodor Kocher and Anton von Eiselberg (5). Prof Heijiro Nakayama, Director of the Institute of Histopathology of the Kyoto Imperial University College, and Prof. Tsunejiro Sakurai of the Department of Anatomy of the same.

Institute highly influenced Dr Hashimoto's later work (5). In 1912, Dr Hashimoto left Japan to study at Gottingen University, Department of Pathology. Due to the outbreak of World War I Dr Hashimoto returned to his homeland in 1915 (4). He graduated in Medicine at Kyushu University in 1917 (4). At the age of 34 years, Dr Hashimoto devoted himself to his family's medical private practice until his unexpected death, due to intestinal typhus in 1934, at the age of 52 years.

The discovery of Dr Hashimoto

As part of his graduation dissertation in 1912, Dr Hashimoto examined thyroid samples from four middle-aged women who had thyroidectomies for goitre and named unique histological features "struma lymphomatosa." Results were published in the German journal "Archiv für Klinische Chirurgie" along with five self-drawn illustrations (6). Dr Hashimoto depicted thyroid gland infiltration by lymphoid cells and the presence of lymphoid follicles with a germinal center, which had never been reported before. In detail, he described four histological features: (i) lymphoid follicles; (ii) changes in epithelial cells; (iii) extensive presence of connective tissue; (iv) diffuse round cell infiltration (6, 7). Despite some parallels, he excluded the diagnosis of Graves' disease due to the clinical differences. He discussed the potential hypothesis of chronic infection, which was not sufficiently supported by available evidence. Riedel's thyroiditis (8) was reported as a possible alternative diagnosis, but lymphatic system hyperplasia was more pronounced than in Riedel's thyroiditis. He even compared his findings with the "Mikulicz' disease", which is a disorder of salivary and lacrimal glands. After extensive analysis of the available literature, he supposed the existence of a specific causative factor responsible for lymphocytic cell expansion, but he declared that "at present moment cannot say anything definitive about the cause" (6, 9).

The impact of Dr Hashimoto's discovery

During his lifetime, Dr Hashimoto did not receive high recognition for his discovery even in Japan, where not much was known about him (10). Cases with similar pathologic findings was reported in 1913 by the German pathologist Simmonds, in the manuscript entitled

"Lymphatic changes in the thyroid gland" (11) and, in 1914, by the German Surgeon Heineke (12). Neither of them mentioned Dr Hashimoto's findings. The disease was for a long time considered an early

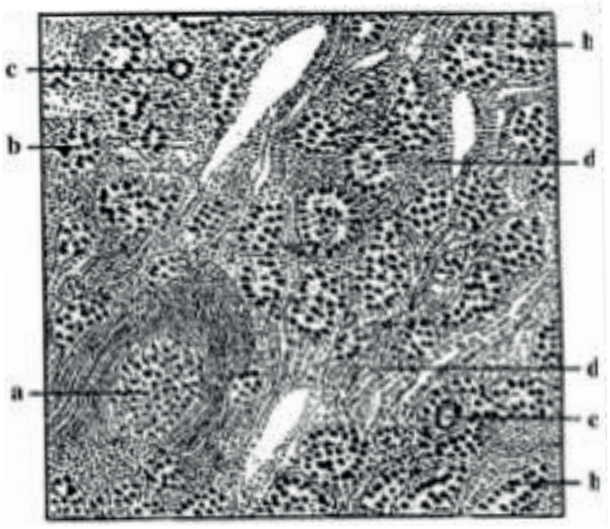

Figure 1. Fourth or fifth cervical vertebrae with post-traumatic interapophyseal arthrosis of *Spinosaurus maroccanus*. Taouz, Morocco, Lower-Middle Cretaceous (Inv. N. 830). Histopathologic picture of struma lymphomatosa, as shown in Figure 5 of the original paper (6). (a): lymphoid follicle; (b): degenerated thyroid follicle; (c): giant cells; (d): hyperplastic interstitium with prominent round cell filtration. Photo taken from Takami et al., 2008 (10).

stage of the already-known Riedel's thyroiditis. Potential reasons for the lack of recognition can be attributed to the use of German language in which the manuscript was written, the rarity of the disease described and, certainly, the outbreak of World War I. As a matter of fact, Dr Hashimoto's manuscript was mentioned for the first time in 1922 by Reist in a review of chronic thyroiditis (13). In the early 30's, the so-called

"struma lymphomatosa" was recognized as an independent disease from Riedel's thyroiditis (14, 15). Since mid-1930s, the name of Dr Hashimoto was linked to the discovery and the term HT was generally used rather than the original struma lymphomatosa. Hertzler, a worldwide famous thyroid surgeon, was one of the principal supporters of Dr Hashimoto's work (16). In 1937, Means also reported Dr Hashimoto as first physician to describe a new disease (17). In 1939 the term "struma lymphomatosa" was used for the first time as a title of a manuscript (18) but afterwards, the disease was universally recognized as "Hashimoto's thyroiditis". Hashimoto's disease received its own complete session during the Third International Thyroid Conference in Washington, DC, in 1938 (9). Unfortunately, in the early 40's the outbreak of World War II impaired medical research; in the post-war years,

HT was still considered a "strange variant" of goiter (19, 9) and surgery remained the main treatment for a long time.

Almost two decades after Dr Hashimoto's discovery, two new publications changed the course of HT. In fact, Rose and Witebsky showed that intravenous injection of purified thyroglobulin into rabbits led to the unexpected formation of thyroglobulin antibodies. Moreover, Rose injected into a rabbit purified thyroglobulin derived from the very same animal and detected not only thyroglobulin antibodies but also thyroidal histological changes similar to those in HT (20, 21, 22). However, the first draft of their manuscript was rejected because the results were judged unrealistic (9). The manuscript was accepted and published sometime later and represented the basis of the concept of organ-specific autoimmune disease. This seminal discovery led Doniach and Roitt to become the first to detect thyroglobulin antibodies in the sera of patients affected by HT, thus proving that HT patients have an immune reaction to human thyroglobulin (22). To note, anti-thyroid antibodies were also detected in the blood tests of patients affected by Grave's disease.

In Japan the terms Hashimoto's disease and Hashimoto's thyroiditis were introduced in the 1950s by Hachinen Akita, a doctor who graduated from same College attended by Dr. Hashimoto (10).

In 1962 a manuscript published by Doniach in The Lancet, titled "letter to the editors", showed for the first time a portrait of Hakaru Hashimoto from 1912 (23) to grant him recognition.

Epidemiology

The diagnosis of autoimmune endocrine disorders, including thyroid autoimmunity disease, has markedly risen in the last years (24). Today, HT is one of the most common causes of hypothyroidism. The etiology of HT is still largely unknown; genetic susceptibility, epigenetic factors and environmental triggers are certainly involved (25, 26). Autoimmune thyroid diseases demonstrate a higher frequency in family members of HT patients and a high concordance in monozygotic twins, confirming the significant role of genetics.

Environmental factors also play an important role, either affecting the population in general, as iodine excess (27), selenium and vitamin D deficiency (28, 29, 30), infective agents, or impacting on the individual risk as in the case of immune-modulatory drugs and stress (26). Indeed, it has been reported that HT has the highest incidence in white individuals, and lowest in black and Asian individuals, probably because of both genetic and environmental factors (31). Sex and age significantly influence HT incidence. In an extensive review of the incidence and prevalence of thyroid autoimmunity, McLeod and Cooper concluded that women have a much greater risk of HT than men and hypothyroidism from Hashimoto's becomes more common with advancing age (24).

Diagnosis, clinical manifestations and treatment

The initial finding in HT is generally a firm, symmetric, painless goiter (Goitrous form) or an atrophic thyroid gland (atrophic form) (2). Patients with HT

typically have high blood thyroid TPOAb concentrations, whereas serum TgAb concentrations are not always detectable. (2). On ultrasound examination, the thyroid gland usually appears hypoechogenic and not homogenous.

Symptoms are related to thyroid hormone depletion (hypothyroidism) due to their influence on most organs and systems, including the heart, respiratory and skeletal systems. Patients affected by hypothyroidism often complain of myalgias, slowness of movements, fatigability, and cramps, which cause a negative impact on their general quality of life (32). Hypothyroidism might cause s hemodynamic changes resulting in dysfunctional control of arterial blood pressure, mainly diastolic hypertension (33).

Levothyroxine (LT4) taken orally every day is the conventional treatment for HT and with a few exceptions, completely resolves signs and symptoms of hypothyroidism in most patients (34). The goal of LT4 (levothyroxine) replacement therapy is the normalization of TSH and FT4 (free thyroxine 4) levels. Patient's demographic features (age, weight), health status (pregnancy, concomitant disorders, such as cardiac disease), general condition along with the degree of hypothyroidism should be taken into account when establishing the introduction of LT4 and the daily dose (34). Since long-term adverse effects of overt hypothyroidism may be expected in subclinical hypothyroidism (2, 33). LT4 administration is suggested also in some cases of subclinical hypothyroidism (2).

Conclusions

The discovery of HT was a significant step in the history of medicine and paved the way toward the discovery of autoimmunity and endocrine disorders. Although significant progress has been made in understanding the contributions of genetic factors and environmental triggers to the development of HT, the exact cause of the disease still awaits clarification. Recent advances in molecular technology will likely provide a better understanding of the relationship between genetic factors and environmental factors in HT and new therapeutic approaches. However, further investigation into disease is much needed to provide more effective clinical targets for treatment.

It just may be the wish of Dr. Hakaru Hashimoto, who received almost no recognition in his life for discovering this disease, that this task is to be accomplished in the near future, thus helping millions of affected individuals.

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