Review

Research Progress on IgG4-Related Hashimoto's Thyroiditis

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Abstract

IgG4-related disease is a systemic autoimmune disease with unknown cause and involves multiple organs and tissues. This disease became one of research hotspots in the last ten years. IgG4-related Hashimoto's thyroiditis (HT) exhibits unique clinical pathological characteristics: serum-free thyroxine reduction and increases in thyroid peroxidase antibody and IgG4; massive IgG4-positive plasmocyte infiltration in tissues; significant matrix fibrosis; and severe degeneration of thyroid follicular epithelium. IgG4-related HT is a subtype of HT; it presents relatively good therapeutic effect after thyroxine treatment. Cortical hormones can be used for IgG4 HT patients who may suffer from hypothyroidism with significant thyroid injury during early stage to constrain immune injury. This thesis summarizes clinical and pathological histology of IgG4-related HT based on its characteristics.

IgG4-related disease (IgG4-RD) is characterized by increased serum IgG4 level, IgG4-positive plasmocyte infiltration, and fibrosis in involved tissues, including multiple organs. Scholars in Japan and the USA carried out studies on correlation between autoimmune thyroid diseases, including Hashimoto's thyroiditis (HT) and IgG4. Results showed unique clinical pathological characteristics of IgG4-related HT. As a unique subtype of HT, this disease gained increasing attention from specialists.

Introduction

HT is also called Hashimoto's disease or chronic lymphocytic thyroiditis. HT is an autoimmune disease of the thyroid, and it was first reported in Hashimoto^[1], Japan in 1912. HT occurs among middle-aged and old women and is probably related to iodine-excess diet, bacterial or viral infection, cytokine therapy, and pregnancy. Clinical features of HT patients include physical symptoms, such as dysphagia, cervical constriction, and goitrous hypothyroidism, or their absence. Thyroid autoantibodies play important roles in pathogenesis of HT. Specific antibodies for thyroid tissues may exist in patients' serum;

these antibodies include thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), and thyroid-stimulation blocking antibody; thus, scholars further studied antibodies based on their categories, serum content, and mode of action and discovered that HT pathogenesis may be related to T-lymphocyte imbalance. Pathological features of HT include tenacious and diffused swelling of the thyroid, diffused lymphocytes under microscopy, plasmocyte infiltration with formation of lymphoid follicle in the germinal center, degeneration and damage of normal thyroid follicular cells, acidophilic degeneration, colloid reduction, and proliferation of fibrous tissues^[2]. HT is not a unitary type of lesion and can be divided into several subtypes according to clinicopathological features. To date, fibrous variant of HT is the most common type and most extensively studied.

IgG4

IgG is one of the five types of human immune globulins and is the main antibody ingredient in sera, accounting for 75% of serum Ig. IgG4 mainly comprises plasmocytes and is secreted in the spleen and lymph nodes. IgG4 features the least content among four IgG subtypes^[3] and a unique

structure and function. In normal individuals, IgG4 accounts for 3%–6% of total IgG in serum, and its content measures 0.01–1.4 mg/ml. IgG4 content is relatively constant in the same individual^[4]. IgG4 cannot effectively activate addiment for itself, and its function in immune response is very limited. However, this condition can be mediated by extended or repeated antigen reactions. IgG4 functions in immune response of T helper (Th) 2 cells. Th2 cytokines, such as IL-4 and IL-13, facilitate IgG4 generation^[3,4].

IgG4-RD

IgG4 represents one of the IgG subtypes, and the correlation between IgG4 and some diseases gradually became an emerging topic in the last ten years. Increase in serum IgG4 only occurs in minor diseases, such as atopic dermatitis, parasitic diseases, and autoimmune bullous dermatosis. In 2001, Hamano *et al.*^[5] discovered that autoimmune pancreatitis (AIP) is related to serum IgG4 increase. Afterward, similar diseases in multiple sites were discovered successively; these diseases include sclerosing cholangitis, interstitial pneumonia, nephritis, retroperitoneal fibrosis, and inflammatory pseudotumor. AIP disease was also discovered in head and neck sites, including salivary, submaxillary, parotid, and pituitary glands^[6]. Diseased regions differed, but high expression of IgG4 was detected in plasmocytes of lesion sites, with manifestation of common features of chronic fibrous inflammation, increased IgG4 in serum, and high-titer autoantibodies. In 2005, Komatsu *et al.*^[7] discovered that approximately 25% AIP patients exhibit hypothyroidism. This incidence started exploration of relationship between IgG4 and autoimmune thyroid diseases.

IgG4 HT

Autoantibodies of thyroid play an important role in HT pathogenesis. In 1980s, foreign scholars analyzed distribution of four IgG subtypes in serum TGAbs and TOPAbs of HT patients. Weetman *et al.*^[8] discovered that majority of HT patients manifest IgG4 overexpression. Parkes *et al.*^[9] discovered that serum TGAbs of HT patients mainly comprises IgG4, whereas TPOAb is mainly composed of IgG1 and IgG4. Research indicated that IgG1 may activate addiment through mediation of antibody-dependent cytotoxic effects and addiment-dependent cytotoxic effects, causing damage to thyroid tissues. IgG4 in serum of patients with thyroid dysfunction and normal

people does not cause damage to thyroid, but it possibly indicates long-term autoantibody exposure, which results in chronic antigenic stimulation. In 2009, Li *et al.*^[10] carried out exploratory IgG4 immunohistochemical staining among 13 HT patients, two subacute thyroiditis patients, and two lymphocytic thyroiditis patients; they were divided into IgG4 thyroiditis group and non-IgG4 thyroiditis group according to IgG4 plasmocyte count and IgG4/IgG plasmocyte specific value after preliminary analysis of difference in clinical features of both groups. In 2010, this research group carried out again immunohistochemical staining among thyroid tissues of 70 HT patients for the first systematic research on characteristics of clinical pathology of IgG4 HT and non-IgG4 HT^[11]. In 2010, Takahashi *et al.*^[12] proposed the concept of IgG4-RD, announcing the birth of this new syndrome. In 2011, Umehara *et al.* from Japan^[13] proposed comprehensive diagnosis standards for IgG4-RD. In existing studies, IgG4 HT accounted for 27.03%–42.42% of HT cases, and differences in proportion may be related to differently obtained diagnosis cutoffs. However, results showed that IgG4 HT was common in HT and should be given clinical attention.

Clinicopathological features

In 2012, Li *et al.*^[14] systematically concluded clinical features of IgG4 HT in subsequent studies. IgG4 HT possibly occurs in females. However, compared with HT, male patients with HT increased. Compared with HT, onset age and surgical age of IgG4 HT are relatively early at an average age of 52. However, disease progression is quick, and this condition can possibly turn into hypothyroidism and is difficult to rectify. Clinical manifestations include unilateral or bilateral swelling of the thyroid with strong but pliable texture. Patients may exhibit fatigue, constipation, dry skin, and loss of appetite but also gain in weight. Current studies failed to discover IgG4 HT complicating IgG4-RDs.

Hematological examination of IgG4 content in serum bears significance in diagnosis of IgG4-RD. High-titer autoantibody is one of remarkable characteristics of IgG4 HT. Tier of IgG4, TgAb, and TPOAb in patient serum increases significantly, whereas free thyroxine may decline accordingly.

Imageological examination and supersonic inspection are the most important iconographic means for diagnosis of thyroid disease. Different from diffused thick echo frequently

shown by non-IgG4 HT group, IgG4 HT shows unilateral lesions or solitary nodule of the thyroid and diffused low echo or mixed echo. Blood flow also increases inside the thyroid.

Pathological alteration of IgG4-RD manifests infiltration of a large number of lymphocytes and IgG4 plasmocytes and notable tissue fibrillation [13]. IgG4 HT displays both characteristics of HT and IgG4-RD, manifesting diffused lymphoplasmacytoid infiltration, visible fibrillation of mesenchyme, and severe degeneration of epithelia on thyroid follicles. Fibrillation among follicles accounts for the majority of symptoms, i.e., hyperplastic fiber texture divides the folliculus thyroid into isolated follicles. Infiltration of lymphoplasmacytoid among epithelial cells on follicle causes degeneration of a large number of follicular cells. Colloid content in follicles reduces or is absent. Obliterating phlebitis may exist. Immunohistochemical staining showed significant increases in populations of IgG4 and plasmocytes, population of IgG and plasmocytes, specific value of IgG4 or IgG, and plasmocytes. Diagnostic criteria include infiltrative IgG4-positive plasmocytes/IgG-positive plasmocytes > 40% and population of IgG4-positive plasmocytes under each high-power lens >10 [15].

Differential diagnosis

To date, IgG4-related thyroid diseases include HT and Riedel's thyroiditis (RT) and may also include subacute thyroiditis. Difficulty arises from clinical identification of these diseases, nodular goiter, and thyroid tumors. Thus, comprehensive diagnosis requires combining clinical manifestations, laboratory examinations, and imageological assessment.

Identification of RT

RT is also called invasive fibrous thyroiditis, which is the rarest type of thyroiditis. Clinical manifestations include hard-texture painless lump in unilateral or bilateral thyroid; this lump is usually fixed because of adhesion with tissues around the thyroid. Lesions may involve the entire thyroid or be limited to local regions with unclear boundary with normal thyroid tissues. IgG4 HT usually features visible diolame showing clear boundary with normal tissues. Different from IgG4 HT, RT patients usually present normal thyroid functions with rare conditions of thyroid hypofunction. Thyroid antibody titer shows no significant

increase. Other types of multifocal fibrotic sclerosis can be complicated; these types include idiopathic retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, and orbital pseudotumor.

Identification of subacute thyroiditis

Subacute granulomatous thyroiditis is also called giant cell thyroiditis. This condition is a self-limited disease, and its pathogenesis is usually related to viral infection. Asymmetric medium enlargement usually occurs in thyroid, specifically the unilateral or bilateral thyroid. Involved sites of subacute granulomatous thyroiditis exhibit pliable texture with nodular shape, white or yellowish white color, irregular edge, and clear or unclear boundary with surrounding normal thyroid tissues. Under microscopy, follicles appear larger than normal and with epithelial proliferation. Monocytes, foreign body giant cells, and epithelioid cells are detected without caseous necrosis. During recovery period, inflammation gradually vanishes, and visible fibrosis can be observed in mesenchyme. Subacute thyroiditis patients show increased IgG4 titer, but most present normal thyroid function without thyroid antibodies in serum.

Identification of nodular goiter

Nodular goiter is the most clinically common thyroid disease and mostly occurs in females with long duration and repeated attachment. Under a microscope, thyroid tissues show different sizes of nodular structure separated by proliferating fibrous tissues. Fibrosis regions may show calcification, cholesterol crystal, lymphocyte, and macrophage infiltration. Under microscopy, samples from patients with such condition show non-visible degeneration of follicular epithelium and necrosis and absence of notable abnormality in serum IgG4 and antithyroid antibodies.

Identification of thyroid tumor

Papillary thyroid carcinoma is the most common malignant tumor in the thyroid without visible abnormality in the major tumor IgG4 and antithyroid antibody. However, HT possibly transforms into papillary thyroid carcinoma. Studies showed that HT patients with papillary carcinoma may feature positive IgG4 expression. Therefore, B ultrasound, cytological examination, and tissue biopsy are adopted to identify whether IgG4 HT patients present papillary thyroid carcinoma.

Treatment and prognosis

To date, glucocorticoid therapy is the footstone for IgG4-RD treatment. However, no recommended standard is available for therapeutic doses. HT patients do not receive treatment when their thyroid functions are normal. Follow-up visit can be provided to HT patients every half to one year to check their thyroid functions. Levothyroxine replacement therapy is adopted for patients with hypothyroidism and subclinical hypothyroidism of thyroid-stimulating hormone >10 mIU/l [2]. Currently, though not widely used, glucocorticoid therapy of HT is mainly used for curing Hashimoto's encephalopathy, alleviating pain, and ameliorating hypothyroidism by local injection. However, abovementioned research indicated that at moderate doses, glucocorticoid therapy can be tested in early-phase IgG4 HT without hypothyroidism to contain reaction of inflammation damage; reversing thyroid damage of HT in early phase does not cause clinical hypothyroidism, which aids in remission and improvement of thyroid function [10]. However, when clinical symptoms reoccur after hormonotherapy, excision should be considered for complete remission.

Prospect

Correlation of IgG4 and thyroid disease is a new significant issue. IgG4 HT is fairly common in clinical practice. Thus, considerable attention should be provided to studies of this condition. Inspection of IgG4 in serum can be conducted to screen thyroid diseases that may initially bear relation with IgG4. Some relatively specific therapeutic methods, such as corticosteroid therapy and biological agents, should also be adopted, and they deserve further discussion. Based on existing studies, further IgG4-related studies must be conducted on other thyroid diseases, such as Graves' disease, RT, postpartum thyroiditis, and connective tissue diseases, through HT cases to provide methods and basis for clinical diagnosis and treatment.

Declarations

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No.

Competing interests

The author declare that she has no competing interest.

Authors' contributions

G Ji made the literature analysis and wrote, discussed and revised the manuscript of this review.

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