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Hashimoto's Thyroiditis – Interactions of Lymphocytes, Thyroid Cells and Fibroblasts

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1. Introduction

Autoimmune Hashimoto's thyroiditis involves painless enlargement of the thyroid, which, in histopathological analysis, is characterised by diffuse lymphocytic infiltrations, fibrosis, and atrophic changes. It is a diffuse process, a combination of epithelial cell destruction, lymphocyte infiltrations, and fibrosis. The incidence of Hashimoto's thyroiditis ranges between 0,3 and 1,5 per 1000 persons. It is diagnosed 15-20 times more frequently in females than in males. The forms of Hashimoto's thyroiditis include: euthyroid goitre, and goitre in subclinical or clinical hypothyroidism, hypothyroidism without goitre, silent thyroiditis, postpartum thyroiditis, alternating hyperthyroidism and hypothyroidism [Weetman &McGregor 1994].

Hashimoto's thyroiditis is often associated with type I diabetes, coeliac disease and other autoimmune diseases. It is one of the components of the autoimmune polyglandular syndrome.

In histopathological investigations of Hashimoto's thyroiditis, the follicular epithelial cells in the thyroid are large and often eosinophilic; they are the so-called Hurthle or Askenazy cells packed with mitochondria. Lymphocyte clusters present between the follicles form typical lymphoid follicles in some sites. Infiltrations contain numerous plasma cells. In Hashimoto's thyroiditis, the immunological attack appears to be destructive, rather than stimulating, as in Graves' disease. Two variants of Hashimoto's thyroiditis have been reported so far: atrophic – related to gene HLA-DR3 inheritance, and hypertrophic – involving goitre enlargement associated with HLA-DR5 [Weetman, 2004]. A study of autoimmune thyroiditis in monozygotic twins demonstrated environmental factors inducing development of the disease [Brix et al., 2000]: high iodine intake, selenium deficiency, smoking, infectious diseases, e.g. hepatitis C, and some drugs [Duntas, 2008]. Prolonged exposure to iodine leads to enhanced iodination of thyroglobulin, which increases its antigenicity and initiates autoimmune processes in genetically predisposed individuals. Selenium deficiency causes a decrease in the activity of selenoproteins, including glutathione peroxidise, which leads to an increase in the concentration of hydrogen peroxide and development of inflammatory processes.

Classical histopathological descriptions of the thyroid in Hashimoto's thyroiditis emphasise the fact that the changes include destruction of thyrocytes, lymphocytic infiltration, and fibrosis.

2. The course of the immune response in Hashimoto's thyroiditis

2.1 Antigen presentation

Stimulation of the immune system depends on maturity of dendritic cells. Immature dendritic cells are characterized by expression of small numbers of co-stimulatory molecules and proinflammatory cytokines; they may also cause anergy. Maturing dendritic cells display significantly higher expression of MHC class II and co-stimulatory molecules, but low levels of proinflammatory cytokines. Only mature dendritic cells can induce regulatory T cells [Jonuleit et al., 2001; Menges et al., 2002; Gad et al., 2003; Wakkach et al., 2005]. Antigen presenting cells are more frequently found in Hashimoto's thyroiditis than in healthy thyroid glands or individuals with non-autoimmune thyroid diseases (simple goitre, non-toxic nodular goitre) [Ben-Skowronek et al., 2008, 2011]. No mature dendritic cells presenting MHC class II antigens have been found in thyroid preparations. The investigations conducted by Kimura et al. have indicated that MHC class II antigens may be expressed on thyrocytes in the autoimmune thyroid inflammation. Our own research has shown a positive reaction with the monoclonal antibody CD1a specific for dendritic cells in some thyrocytes. This is not sufficient to initiate the autoimmune response, but sufficient to sustain it [Kimura et al., 2004].

2.2 Development of immunological reaction in the thyroid gland

Lymphatic follicles appear inside the thyroid gland in the course of Hashimoto's thyroiditis. The study of Armengol et al. has demonstrated higher levels of lymphokines and their ligands responsible for lymphocyte migration, settlement, and formation of lymphoid follicles (lymphotoxin α, lymphotoxin β, CC chemokine ligand (CCL)), and CXC (CXCL 12, CXCL13) chemokine ligands). Moreover, in response to inflammatory cytokines, thyrocytes can produce CXCL12. Tissue stress caused by viral or bacterial inflammation is likely to lead to formation of lymphoid follicles in the thyroid [Armengol, et al., 2003]. Production of cytokine ligands for CXCL21, CXCL 22, and CXCL 13 by thyrocytes is correlated with the level of anti-thyroid antibodies, and thus, directly with the inflammatory response in the thyroid [Armengol et al., 2003].

From the physiological point of view, lymphoid follicles are small structures in which processes of somatic hypermutation, maturation of immune affinity receptors, switching of antibody isotypes (e.g. from IgM to IgG), and receptor control take place. Autoreactive T cells arise de novo in the germinal centres; here operates the mechanism sustaining tolerance - apoptosis of autoreactive lymphocytes [Pulendrav et al., 1997, Janevay et al., 2002]. In autoimmune diseases of the thyroid, muscles, and joints as well as in Sjögren's syndrome and autoimmune alveolitis, the ectopic lymphoid tissue is arranged in lymphoid follicles in non-lymphatic organs, which do not contain physiological, growing lymphoid tissue [Crawford et al.1983, Schroeder et al., 1996, Wallace et al.1996, Shione et al 1997, Stott et al 1998, Itoh et. al 2000, Sims et al,. 2001]. The function of this lymphoid tissue, sometimes defined as tertiary lymphoid tissue (primary tissues - thymus and bone marrow, secondary - lymphatic glands and organs), is unclear [Weetman et al. 1994, Ruddle et al. 1999, Armengol et al , 2001]. The structure of the ectopic lymphoid follicles in the thyroid is similar to that of typical lymphoid follicles in lymphoid organs: they consist of a germinal centre and a peripheral zone (mantle zone) containing lymphocytes B and T, and dendritic cells. An analysis of immunoglobulin gene rearrangement (RAG1 and RAG2) has confirmed the possibility of formation of high endothelial venules in lymphoid follicles and production of

cytokines responsible for lymphocyte migration and settlement, which would trigger an autoimmune reaction [Armengol et al., 2001]. TG Ab, TPO Ab and TRAK anti-thyroid antibodies are produced in B cells in the lymphoid follicles [Armengol et al., 2001]. High levels of antibodies against thyroglobulin (TG Ab) and thyroperoxidase (TPO Ab) are detected in the serum of patients with Hashimoto's thyroiditis. These antibodies are regarded to have cytotoxic activity. However, investigations of thyroids of foetuses from mothers with Hashimoto's thyroiditis did not show the expected damage. Hypothyroidism was observed only in some children.

T cells originating from mice immunized with TPO strongly react with sequence 540-559; immunisation of mice with this peptide results in development of hypothyroidism and thyroiditis. Peptide 540-559 is probably a key factor in the immune response against TPO [Kawakami et al. 1992]. Natural *HLA-DR-associated peptides* have also been identified; they are present in the colloid, and some of them derive from thyroglobulin [Ng et al., 2006]. A larger proportion of lymphocytes binding to thyroglobulin are present in the thyroid than in peripheral blood [Heuer et al., 1996]. Being the major stimulatory antigen, thyroglobulin is indispensable for T cell response [Sugihara et al., 1993]. The severity of autoimmune reactions following immunization with thyroglobulin has been observed in transgenic mice producing IL-12 [Kimura et al.,2005].

Immune reactions involving T cells are controlled by certain T lymphocyte subpopulations: CD4 + Treg and natural killer lymphocytes are employed in the control of the magnitude and class of the immune response, while lymphocytes CD8 + are responsible for recognition for self- and non-self- antigens [Jang et al., 2006].

A slightly larger number of CD4 + cells have been observed in Hashimoto's thyroiditis than in non-autoimmune thyroid diseases; however, the number was statistically significantly lower than in Graves' disease [Ben-Skowronek et al., 2007,2008]. The studies of McLachlan suggest that the reduction in the number of Treg cells (particularly CD25) induces lymphocyte infiltration in the thyroid accompanied by transient or permanent hypothyroidism [Mc Lachlan et al., 2007].

Animal studies have shown that depletion of CD4 + CD25 + Treg in mice increases susceptibility to thyroiditis by enhancement of the immune reaction against thyroglobulin and exacerbates the existing thyroiditis, whereas an increase in the number of CD4 + CD25 + T cells restores resistance to thyroiditis [Morris et al., 2006,2007, Nagayama ey al. 2007]. It appears that an insufficient percentage of CD4 + T cells in Hashimoto's disease is the cause of the destructive autoimmune reaction in the thyroid.

Suppressor/cytotoxic lymphocytes CD8 + have been found among thyrocytes in thyroid follicles, in lymphatic infiltrations and in the lymphoid follicles of the mantle zone. Glycoprotein CD8 present on the surface of cytotoxic lymphocytes may bind to the class I MHC molecule, which leads to activation of T cells CD8+. This activation is also dependent on co-stimulatory proteins binding to antigen CD28 (the so-called two-signal model). Once activated, cytotoxic lymphocytes may secrete cytotoxins, and granzymes and granulysins. They perforate the cell membrane and form pores, which induces apoptosis of the target cell. Another pathway leading to apoptosis is activation of the Fas ligand [Iannacone et al., 2005,2006, Subramanian et. al., 2005]. Hypothyroidism in patients with autoimmune thyroiditis is associated with apoptosis of alveolar epithelial cells induced by cytokines. Expression of Fas ligand on thyrocytes of patients with Hashimoto thyroiditis and a weak reaction for Bcl-2 have been detected, which suggests cytokine-induced apoptosis [Kawakami et al., 1996, Mitsiiades et al.,1998, Stassi et al., 2002]. TPO-specific T cells cause

destruction through cytotoxic mechanisms involving CD4+ and CD8 + cells or programmed Fas- TNF-alpha-induced apoptosis [Stassi et al., 2002]. In Hashimoto's disease, damaged thyrocytes in contact with CD8 + T lymphocytes may be observed in the light microscope. The electron microscopy has shown contact sites of lymphocytes with thyrocytes located in the thyroid follicular epithelium. Polarization of endolysosomes near the site of contact has been detected in the lymphocytes which displayed the T-cell phenotype of and CD8 + location. Similar observations of cultured CD8 + and dendritic cells in experimental conditions were conducted by Gardella et al. [Gardella et al., 2001]. The studies of Negrini et al. [Negrini et al.,2006] have indicated possible presence of the GITR (Glucocorticoid-Induced TNF-Like Receptor) antigen on the surface of CD8 + T cells, which would render them as regulatory Treg cells. Therefore, it is believed that cytotoxic T cells, K (killer) lymphocytes, NK (natural killer) cells, and regulatory (Treg) or suppressor T cells may play an important role in autoimmune thyroid damage. Some studies indicate the ability of T cells to transfer thyroid autoimmune processes, both in animals with experimental autoimmune thyroiditis and patients who have undergone bone marrow transplantation [Kawakami et al.,, 1992, Ng et al., 2006, Drabko et. al., 2006].

Active lymphocytes B CD79alfa+ and antibody-producing plasma cells were found in a small percentage of thyroids from healthy children (4,11%), in the colloid goitre (1,83%) and the nodular goitre (5,22%). The largest number of CD79 alpha+ lymphocytes was observed in thyroid specimens from patients with Hashimoto's thyroiditis (average 31,65%) In lymphatic infiltrates, plasma cells constituted almost half of the cells (46,67%), and amounted to 17,23% in the thyroid parenchyma. Foci of damaged thyroid follicles and numerous fibroblasts and collagen bands have been observed at the plasma cell accumulation sites. The thyroid glands in children with Hashimoto's thyroiditis displayed characteristics of lymphocyte activation, the so-called blastic transformation, consisting in an increase in the volume of the cell and, particularly, of the nucleus, appearance of nucleoli and an increase in the cytoplasm volume through enlargement of the rough endoplasmic reticulum, in which antibody production takes place [Ben-Skowronek et al., 2007].

Thyrocytes in Hashimoto's thyroiditis are cuboidal or flat. The thyroid cells exhibit damage. Cell nuclei are often folded; secretory vesicles are sporadically present in the apical pole (sometimes there are no vesicles); and swollen mitochondria are present in the basal pole. The swollen part of thyrocytes without microvilli or with single microvilli projects into the lumen of the follicle. The basal membrane is thickened. Plasma cells, lymphocytes and fibroblasts are visible among the thyroid follicles. At the lymphoid infiltration sites, the lymphoid cells separate the thyroid epithelium from the basal membrane of the capillary blood vessels. Lymphocytes are often in direct contact with plasma cells. Plasma cells filled with concentrically arranged layers of the rough endoplasmic reticulum adhere to the basal membrane of the thyroid follicle and the surrounding thyrocytes. The thick, electron dense basal membrane contains numerous collagen fibres. The adjacent cytoplasmic membrane does not exhibit characteristic folds. The fibrous basal membrane hinders blood flow in the capillary blood vessels and deformed erythrocytes can be seen in their lumen. The exchange of nutrients and oxygen between thyrocytes, the interstitium, and blood vessels is impeded [Fig. 1].

3. Apoptosis in autoimmune thyroid diseases

Apoptosis is a physiological form of cell death resulting from the need of multicellular organisms to maintain balance between dividing and dying cells. Typical morphological
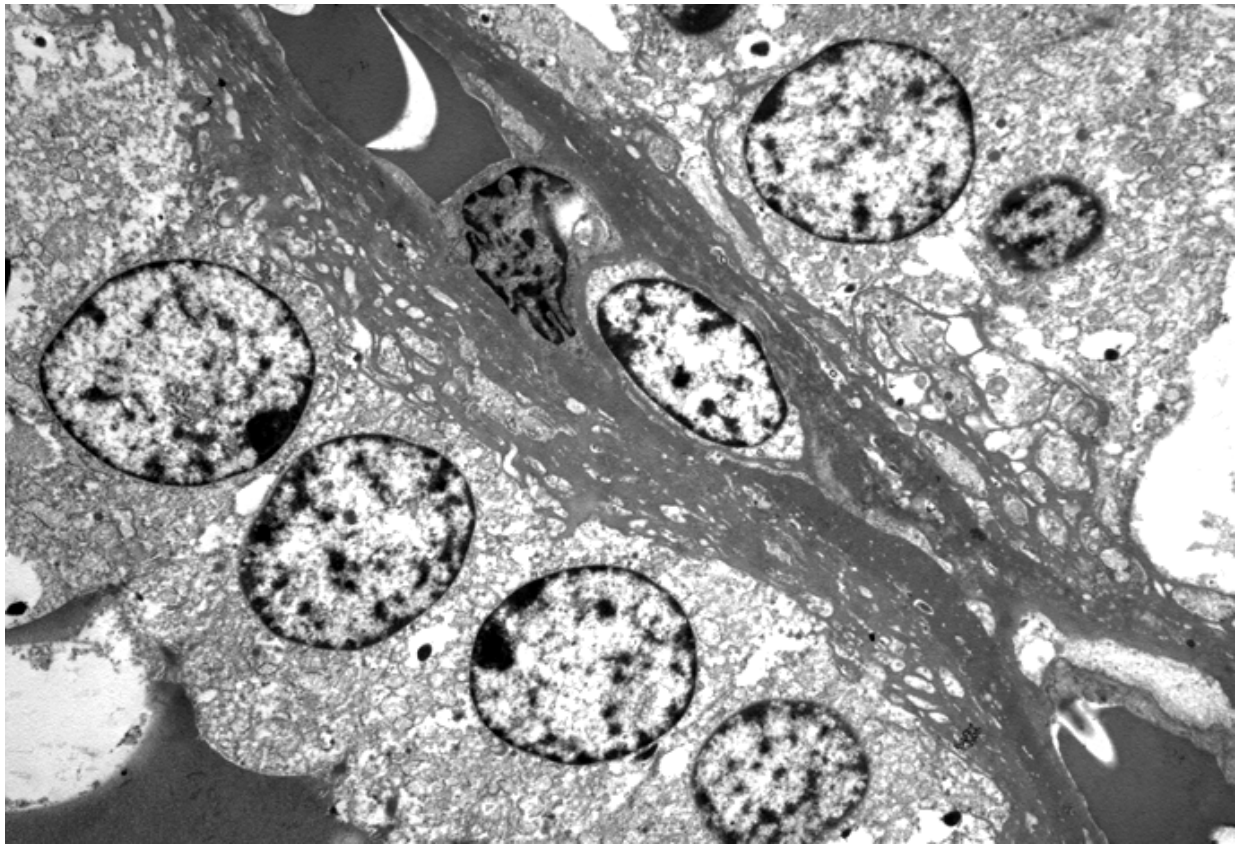
Fig. 1. A markedly thickened basal membrane of the thyroid follicle containing collagen fibres impedes thyrocyte contact with the capillary vessel lumen. In the basal membrane is present lymphocyte (phenotype lymphocyte T). The thyrocytes exhibit signs of damage of thyroid follicular cells– swollen mitochondria, dilated cisterns of the rough endoplasmic reticulum, absence of secretory granules, and atrophy of microvilli. Transmission Electron Microscope Magn. 10 000x.

changes in cells that received the signal to begin the apoptotic process include folding of the cell membrane, condensation of cytoplasm and cellular organelles, disappearance of the mitochondrial membrane, shrinkage of the nucleus, and condensation of chromatin [Yamazaki et al., 2000, Lorenz et al., 2005].

Apoptosis can be initiated by T cells through two pathways:

- by perforins secreted by lymphocytes into the junctions between lymphocytes and target cells; they perforate the cell membrane and form pores thus inducing osmotic lysis of the cell; simultaneously, granzymes B activate the caspase cascade, which leads to cell apoptosis;

- the Fas ligand and TNF-related apotosis induced ligand (TRAIL) secreted by lymphocytes stimulate the so-called death receptors on the cell surface causing activation of caspase cascade through caspase 8 and 10.

Lymphocytic infiltration and antibodies secreted by plasma cells lead to destruction of thyrocytes, but actively stimulate the production of collagen by fibroblasts. As a result, large amounts of collagen accumulate in the follicular and vascular basal membranes. In the final stage of the process, thyrocytes are destroyed via apoptosis. Typical signs of cell apoptosis are visible: chromatin condensation in the nuclei of thyroid epithelial cells, condensation of the cytosol and swelling of the mitochondria [Fig.2].
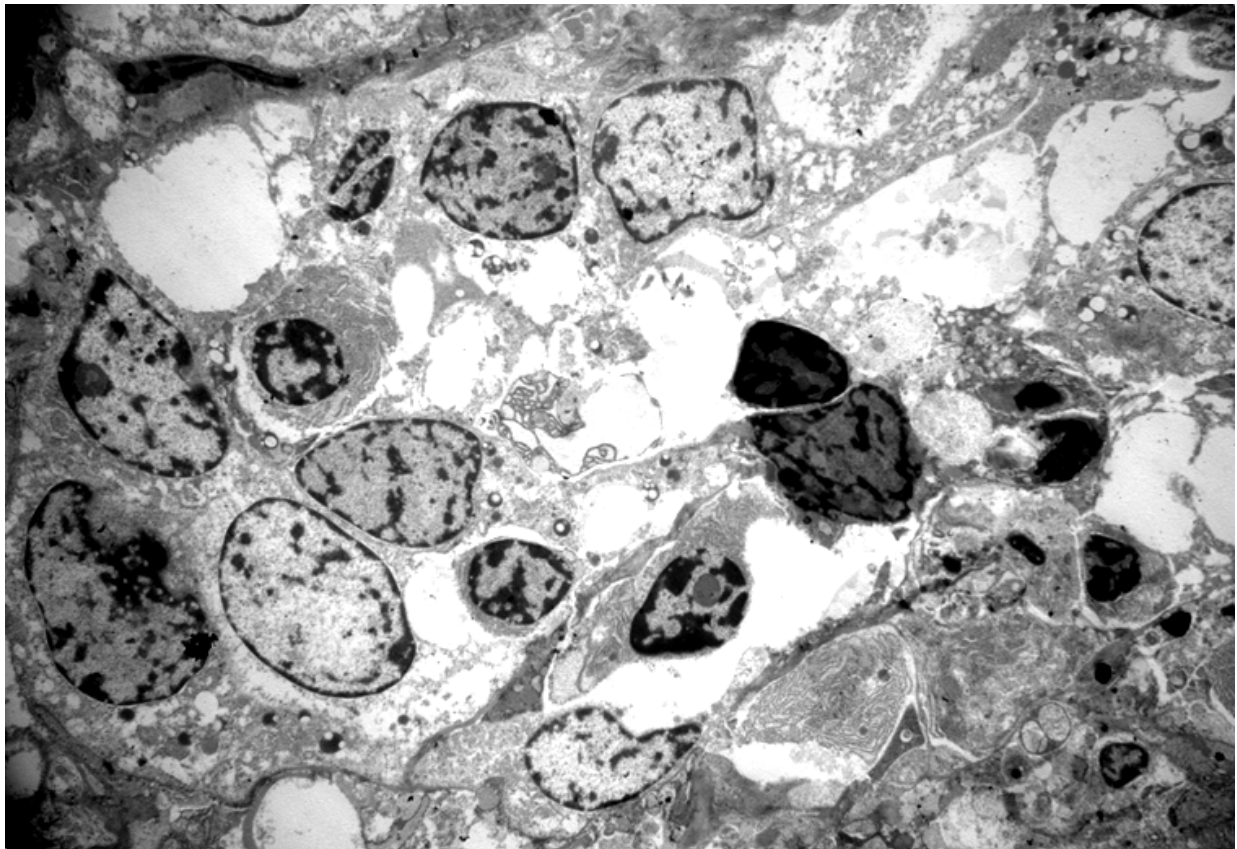
Fig. 2. The last phase of destruction of the thyroid in Hashimoto's thyroiditis. The thyrocytes are damaged due to apoptotic processes. Plasma cells and lymphocytes predominate in the interstitium. The fibroblast migrates to this place and produces collagen fibres. Transmission Electron Microscope. magn. 5000x.

Various phases of thyrocyte death were visible at the lymphocyte infiltration sites; apoptosis was caused by active plasma cells and lymphocytes of the large granular lymphocyte phenotype (LGL) [Fig.2] Ultrastructural investigations have revealed that the reaction between lymphocytes and plasma cells producing antibody results in thyrocyte damage, which, in turn, changes the permeability of cell membranes and intracellular membranes and leads to accumulation of water in the endoplasmic reticulum cisterns in the mitochondria and cytoplasm. Consequently, the cell is enlarged, microvilli disappear, and swollen mitochondria occupy the basal pole of thyroid cells causing cell staining with acidic dyes. At the same time, electron-dense substances (probably antibodies) are deposited in the follicular basal membrane. In response, large amounts of collagen are secreted around the damaged follicles. Communication between the lumen of capillary vessels and thyrocytes is impeded; hence, the transport of oxygen, nutrients, and substrates for production of thyroid hormones is inhibited. The thyrocyte metabolism is decelerated, and production of hormone and protein colloid is disrupted. Thyrocytes gradually die and exfoliate into the follicle lumen. Lymphocytes migrate to replace them and form lymphoid follicles. Fibroblast bands producing collagen fibres penetrate the site as well.

The contact between lymphocytes and thyrocytes in Hashimoto's thyroiditis forms an immunological synapse, which has been described as a specialized intercellular connection between T cells and antigen presenting cells [Paul et al., 1994, Dustin et al., 1999, Grakoui et al., 1999].
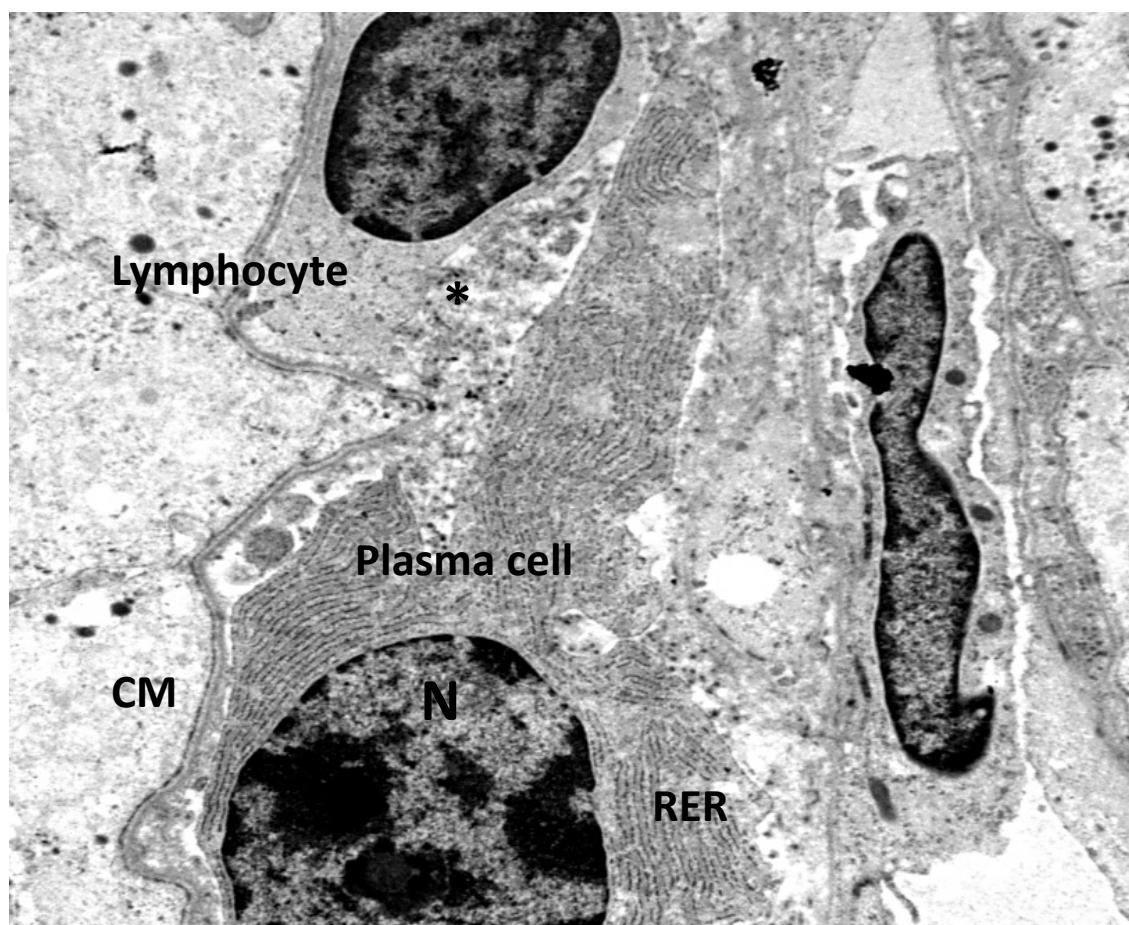
Fig. 3. Junction between the lymphocyte and plasma cell in Hashimoto's thyroiditis. Electron-dense (probably protein) substance is visible in the intercellular space. N – cell nucleus, RER - rough endoplasmic reticulum, L – lysosome, CM – cell membrane. Transmission Electron Microscope magnification 25 000x

The immunological synapse consists of a central zone containing antigen receptors and a surrounding ring of adhesion molecules [Dustin, 2002]. Lymphocytes form projections – lamellipodia – and form junctions with the cell membrane of thyrocytes. Presumably, it is at these sites that antigen presentation by thyrocytes occurs [Bromley et al., 2001]. Recent studies demonstrate different types of immunological synapses: cytotoxic [Dustin et al., 2010] and transitory (the so-called kinapses) [Dustin et al. 2007, 2010]. Observations of the interaction between lymphocytes and other thyroid cells in the course of AITD indicate possible formation of analogous junctions between thyrocytes and lymphocytes, i.e. cytotoxic synapses in Hashimoto's thyroiditis. This implies that lymphocytes secrete granzymes and other cytotoxic substances leading to cell damage.

The junctions of plasma cells with thyrocytes are large adhesion zones with thyrocyte apoptosis visible nearby [Fig.3]. The junctions between plasma cells and fibroblasts, however, are associated with production of collagen fibres. In Hashimoto's thyroiditis, numerous junctions between lymphocytes and plasma cells in the form of adhesion zones and spaces have been detected, into which medium electron-density substances (probably proteins) were secreted [Fig.3]; there are also synapses between young and mature lymphocytes T and B in the lymphoid follicles.

Such cell junctions occur mainly in the lymphoid nodes. Very tight junctions are visible between lymphoblasts and B cells, which are phenotypically similar to plasma cells. Immunological synapses have been found also between lymphocytes [Ben-Skowronek in press]

In Hashimoto's disease, activation of apoptotic processes is also associated with activation of Th1 cells, which enhance the activity of caspase and apoptosis through production of IFN-γ. While reduction in the number of CD4 + cell subsets in the thyroid parenchyma has been reported both in our own study and in animal models of the disease [Sugihara et al., 1993], an increase in the number of active CD4 + IL-4 + was observed in the peripheral blood [Maziotti et al., 2003]. However, no correlation has been found between the number of CD4 + T cells in the thyroid and the antiperoxidase antibody levels in serum [Watanabe et al., 2002, Pandit et al., 2003].

Antibody-dependent cell-mediated cytotoxicity (ADCC) plays an important role in development of Hashimoto's thyroiditis, whereas complement-dependent cytotoxicity (CDC) exerts a lesser effect. The thyroid peroxidase antigen evokes the reaction [Czarnocka et al., 1985, Estienne et al., 2002, Guo et al., 2005 Rebuffat et al., 2006, Ng et al., 2004, 2006]. TPO Ab has been detected in 90% of Hashimoto's thyroiditis patients [Rappaport et al., 2001]. Anti-TPO antibodies are various isotypes of the IgG antibodies. Anti-peroxidase antibodies TPOAb can damage thyrocytes through the ADCC and CDC mechanisms. The cytotoxic ADCC mechanism depends on the interaction between the target cell, antibody and effector cell. Monocytes, which due to FcγRI receptors are effector cells activated by TPOAb, can affect T cells and lead to destruction of thyrocytes [Rebuffat et al.,2008]. FcγRIII are present on Natural Killer cells and FcγRII on monocytes and neutrophils. All FcγR fragments are involved in the ADCC reaction [Rebuffat et al., 2008]. The investigations of Giancotti and Williams et al. suggest that integrins β2 may participate in cytotoxic reactions involving FcγR [Giancotti et al., 1999, Williams et al., 1999]. The study of Rebufatt et al. [Rebuffat et al., 2008], however, indicates involvement of two monocytic cell lines in this process.

It has not been sufficiently documented yet whether specific IgG antibody subclasses take part in thyrocyte damage [Metcalfe 1997, Guo 1997]. Xie L-D et al. investigated the occurrence of anti-TPO IgG subclasses and found that IgG1 was present in 70.2%, IgG2 in 35.1%, IgG3 in 19.6%, and IgG4 in 66.1% of patients; increased proportion of IgG2 predisposes to thyroid damage and hypothyroidism [Xie et al., 2008].

Metcalfe et al. found no correlation between the IgG subclasses and thyrocyte damage in vitro [Metcalfe et al., 1997], whereas Guo et al. demonstrated that thyrocyte damage is associated with subclass IgG1 [Guo et al., 1997]. Recent studies conducted by Rebuffat et al. [Rebuffat et al., 2010, Pappenwali et al., 2010] indicate that anti-TPO antibodies exhibit moderate activity in the ADCC process and can be used in the new methods of treatment of papillary thyroid cancer, the cells of which show expression of TPO.

Thyrocyte damage continues and is potentialized by the CDC reaction [Rebuffat et al., 2008]. Complement component C4, hyperexpressed on the surface of thyrocytes in Hashimoto's thyroiditis, participates in this reaction [Blanchin et al., 2003]. The key antigen here is thyroid peroxidase. The TPO ectodomain consists of a long module similar to myeloperoxidase, followed by a module similar to the complement control protein (CCP) and a module similar to the epidermal growth factor (EGF). The CCP contains a fragment that activates the complement. Therefore, TPO can activate the complement cascade without the help of immunoglobulins. Tg Ab antibodies do not fix the complement [Weetmann et al.,

2004] and probably are not directly involved in the CDC reaction, which is related to the fact that thyroglobulin is not expressed on the surface of thyrocytes.

Reduction or loss of intercellular communication in the final phase of Hashimoto's thyroiditis may lead to destruction of thyrocytes and hypothyroidism [Greek et al., 1996, Green et al., 1997, DiMatola et al., 2000]

- Fibrocytes and fibroblasts in autoimmune thyroid diseases

Fibrocytes and fibroblasts are frequently disregarded in analyses of autoimmune reactions in the thyroid. Ultrastructural studies have revealed significant participation of fibroblasts in the pathogenetic processes in Hashimoto's disease. They enter the space between the basal membrane and thyrocytes and produce substantial amounts of collagen, thus leading to thickening of the basal membrane and impeded contact between the capillary vessel lumen and thyrocytes [Fig. 1,2].

Influx and proliferation of lymphocytes in the thyroid as well as production of collagen is a response to inflammation processes and a stimulus for further thyrocyte damage through isolation thereof from oxygen and nutrients in the blood vessels. Progressive damage of thyrocytes leads to release of large amounts of autoantigen and triggers the inflammatory response. Own observations indicate a possible direct impact of plasma cells, lymphocytes and fibroblasts, since thyroids of Hashimoto's thyroiditis patients exhibit close contact between the groups of lymphocytes, plasma cells and fibroblasts.

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