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DYNAMIC CHANGES IN THE HISTOMORPHOLOGICAL STRUCTURE OF THE THYROID GLAND OF RATS AGAINST THE BACKGROUND OF EXPERIMENTAL AUTOIMMUNE THYROIDITIS

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Abstract

In preclinical studies, which are conducted to study the therapeutic effectiveness and pharmacological safety of biologically active compounds for the correction of autoimmune thyroiditis, various experimental models of this pathology are used in the experiment.

In this work, we analyzed various models of thyroiditis that have been used for the past fifty years. Such an analysis made it possible to choose the most optimal model for the study of autoimmune pathology of the thyroid gland as well as for the correction of this condition. The analysis of known and the search for new pathogenetically justified models of autoimmune diseases of endocrine organs is a very urgent task.

The aim of the work was to study the dynamics of changes in the histomorphological structure of the thyroid gland when modeling autoimmune thyroiditis in rats using an allogeneic antigen isolated from the human thyroid gland.

The postoperative thyroid gland of a person was used as an antigen. Morphological changes in the thyroid gland were studied one, three and six months after the end of the simulation.

It was found that the use of this type of immunization led to changes in the parenchyma of the gland, characteristic of autoimmune thyroiditis. Already one month after modeling, Gürtle cells, fibrosis, areas of lymphoid infiltration of the parenchyma were registered. These pathological changes persisted and worsened three and six months after the end of the simulation.

The investigated type of model of experimental autoimmune thyroiditis is easily reproduced. Pathological changes in the gland deepen over time and are comparable to those that occur in people with Hashimoto's thyroiditis.

Keywords: experimental autoimmune thyroiditis, antigen, lymphocytic infiltration, Gürtle cells, thyroid gland.

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1. Introduction

Autoimmune thyroiditis (AIT) occupies a leading place among the diseases of the thyroid gland. Approximately 3–5 % of the population has this disease [1–6]. AIT is a multifactorial disease. The pathogenetic mechanisms of the disease are not fully known and are very contradictory, there are also no clear symptoms and objective methods of diagnosis and treatment [7].

AIT belongs to an organ-specific autoimmune disease that leads to partial or complete destruction of the thyroid parenchyma and the development of characteristic morphological changes and secretory instability. The only specific feature of AIT today is a certain type of morphological changes in the gland, which is characterized by atrophy of parenchymal cells, fibrosis, an increase in the number of oxyphilic cells (Gürtle cells), as well as diffuse lymphoid infiltration of the thyroid parenchyma, which occurs because of autoimmune factors [8].

In the pathogenesis of autoimmune diseases, the undoubted role according to the literature is given to cytokines that cause tissue destruction on their own or through the activation of autoreactive and inflammatory cells. These include enzyme-linked immunosorbent nucleotides and tumor necrosis factor, which are produced by intrathyroid mononuclear cells. The number of these

cytokines in AIT increases in comparison with the norm. Despite the fact that the hypothesis of the occurrence of AIT is more than 20 years old, the study of the development of autoimmune diseases of the thyroid gland is relevant to this day. The essence of the hypothesis lies in the presence of a partial defect in immunological surveillance associated with a specific deficiency of T-lymphocytes-suppressors, which allows the presence of a forbidden clone of organ-specific T-lymphocytes that interact with antigens, have a damaging effect on target cells, and trigger a localized immune process by the type of delayed type of hypersensitivity. Antigenic stimulation of T-lymphocytes from target cells causes a blast transformation reaction followed by cell division. In this case, cytotoxic mediators are released. T-helper lymphocytes act on B lymphocytes, which turn into plasma cells and form antibodies that affect the structure of the thyroid gland [9].

If the production of antibodies goes beyond the physiological norm, and these changes continue for a long time, then autoimmune reactions go from the category of regulatory to the category of pathological. This becomes the cause of the disease [10, 11].

Based on the above, it is very relevant to develop adequate experimental models of AIT, which would allow to investigate the necessary morphofunctional aspects of AIT and assess the preclinical effectiveness of therapeutic and preventive measures.

To date, there are many ways to model the autoimmune process in the thyroid gland. It primarily uses various forms of thyroglobulin (antigen) mixed with full Adjuvant Freund, which are administered to rabbits, mice, and rats [12–24]. As an antigen, thyroid homogenate is used allogeneically or xenogenically.

The authors of one of the very first developments of AIT modeling protocols (Rumball, Weigel) described immunization models with Freund adjuvants with the addition of: heterogeneous thyroglobulin (Tg) (in which there is a significant activation of *T*-lymphocytes); and with homogeneous thyroglobulin (minimal activation of the level of *T*-lymphocytes). When using this protocol, heterogeneous and homogeneous Tg induced serum antibody levels equivalent to immunized Tg. However, when incomplete Freund's adjuvant was administered, homogeneous Tg induced fewer antibodies than heterogeneous Tg. Even more differences in serum antibody levels to heterogeneous and homogeneous Tg were evident after immunization with soluble Tg. These differences in thyroiditis may be explained by the presence of only a minimal level of competence of T cells to homogeneous Tg, which can induce experimental autoimmune thyroiditis with strict immunization protocols with sufficient frequency.

For modeling AIT, certain lines of mice C57BI/6J are also used. Thus, it was revealed that mice of the line (C57Br/cd) have a good immunological response to immunization, they have a high titer of antibodies to Tg was determined as early as the seventh day, and the first recognitions of lymphocytic infiltration on the fourth day. Unlike line C57BL BL/10, in which antibodies to Tg were not produced at all, nor did destructive changes in the gland occur.

It is believed that AIT induced in mice by immunization with mouse Tg with the addition of a complete Adjuvant Freund, is an adequate model for studying the pathogenesis of chronic thyroiditis (Hashimoto) in humans.

The main issues that need clarification are the difference between regulatory autoimmunity, which is characterized solely by the formation of autoantibodies to Tg, and pathological autoimmunity in which thyroid cells are destroyed. The balance of cytokines that are released at an early stage of the autoimmune reaction most likely determines the transition of the regulatory form of autoimmunity to pathological.

2. Materials and Methods

The studies were conducted in the Laboratory of Pharmacology of the Department of Experimental Pharmacology and Toxicology of the V. Y. Danilevsky Institute of Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine on male rats of the Vistar population (n=32).

Experimental AIT in rats was induced by immunizing animals with human thyroid (thyroid) antigen extracted suboperatively, in combination with Freund's complete adjuvant [12, 15, 25].

Isolation of human thyroid antigen:

− human thyroid tissue extracted supportively was homogenized in three volumes of NaCl and placed for a day in the refrigerator;

− the obtained and settled homogenate was centrifuged for 10 min. at 10–12 thousand rpm.

Immunization of rats was carried out as follows: 0.05 ml of antigen per 100 g of body weight of the rat was mixed with 0.05 ml of the total adjuvant of Freund.

The mixture was injected subcutaneously into the base of the tail. At the same time, experimental animals were given intraperitoneal injections – 0.1 ml of antigen diluted in a ratio of 1:5 NaCl. To obtain persistent AIT, four immunizations were carried out 1 time per week. According to hormonal and immunological studies, thyroiditis began to develop a week after the first procedure, which was confirmed by immunological studies.

Thyroid samples for light-optical examination were withdrawn 1, 3 and 6 months after the end of immunization.

The extracted thyroid glands were fixed in a 10 % solution of neutral formalin, dehydrated in alcohols of increasing concentration, poured into paraffin. Sections of paraffin blocks were obtained using a sledge microtome, stained with hematoxylin and eosin [1]. For the convenience of comparing the morphofunctional state of the thyroid glands of animals of different experimental groups on micro preparations using the Toupcam Granum program, the height of the follicular epithelium and the diameter of the follicles (μm) were measured, the number of thyrocytes in the follicle wall was counted. Statistical processing of the results was carried out using a non-parametric analogue of one-factor dispersion analysis – the Kruskal-Walys criterion, after which the criterion was applied. Mana-Whitney [3−5]. To determine statistical discrepancies, the standard software package Statistical 5 was used. Micropreparations were examined under a Granum microscope. Microphotographs of images were carried out with a Granum DCM 310 digital video camera. Photos were processed on a Pentium 2.4 GHz computer using the Toup View program.

3. Results and discussion

The structure of the thyroid gland of intact rats is a connective tissue capsule surrounding the gland, it is thin, distributes the gland into lobules consisting of follicles. Arterioles, veins and lymphatic vessels are located in the interlobular connective tissue. Capillary vessels of perifollicular normal blood filling.

Thyroid follicles of different sizes, mainly rounded or slightly oval, with clear contours. In the central zone of particles, medium and small follicles predominate, larger follicles are found on the periphery. Intracellular thyrocytes (lining the lumen of the follicles) are mainly cubic in shape, in large follicles – moderately flattened. Follicular thyrocytes are arranged in a single layer. The nuclei of cells are dense, rounded, centrally located.

The space of the follicles is filled with a moderately variable in density oxyphilic colloid. As a rule, the colloid filled the entire cavity.

Follicle. Outside the follicles, there are small clusters of interfollicular thyrocytes in the form of islets, both delimited from the wall of the follicles and merged with them (**Fig. 1**).

Morphometric measurements showed that the diameter of the follicles was 36.7 μm, the height of the thyrocytes was 5.5 μm. The number of cells in the row did not exceed 107.

1 month after the end of immunization of rats with human thyroid antigen in combination with a complete Adjuvant of Freund in the thyroid gland of rats, microscopically detected areas with proliferation of the epithelium and a slight accumulation of colloid in the follicles (with one or another fluctuation in severity). The colloid itself is weakly colored, reticulated.

There were also “empty” follicles. Most follicles are medium to small in size. The thyroid epithelium, which lines the follicles (with a clear certainty of the latter), was predominantly highly cubic. Papillary growths are unevenly expressed in different follicles. follicles were found almost completely filled with branching papillary growths, in others only an increase in epithelial cells in a row or several rows of epithelium was noted. In microfollicles, epithelial proliferation was not observed. In different places of the particles (in the interfollicular stroma), moderate focal lymphoid infiltration was detected (**Fig. 2**).

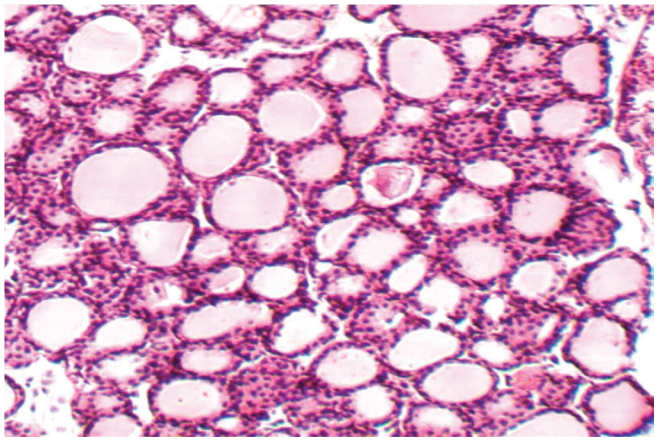

Fig. 1. Thyroid gland of an intact rat. Normal follicular structure of the tissue. Hematoxylin-eosin, ×200

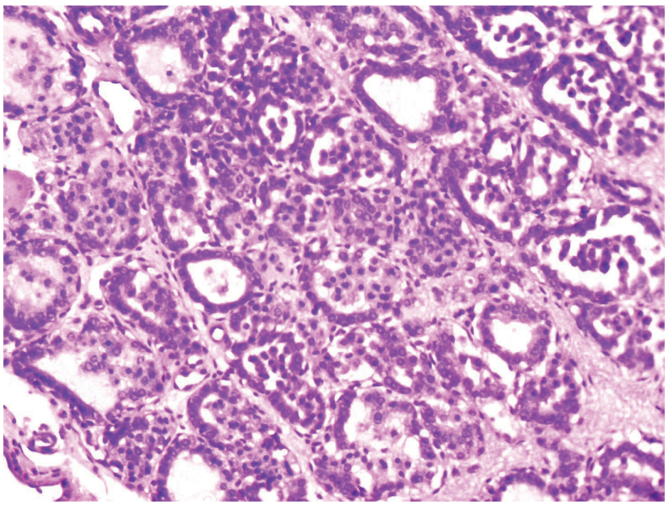

Fig. 2. Thyroid gland of rats 1 month after the end of immunization with human thyroid antigen in combination with a complete adjuvant of Freund. Uneven proliferation of epithelium in different follicles, moderate focal lymphocytic infiltration of the stroma. Fibrosis of individual interlobular connective tissue layers. Hematoxylin-eosin, ×250

Quite often there were Ashkenazi-Gürtle cells, partially or completely lining the follicles. These cells are much larger than typical thyrocytes, with a pronounced oxyphilic cytoplasm, a large, sometimes unusually shaped nucleus (**Fig. 3**).

According to morphometric measurements, the diameter of the follicles did not significantly decrease (on average it became 33 μm), the height of the follicular cells increased slightly (up to 6 μm), the number of epithelial cells in the follicle wall increased to 14 cells. Thus, in the thyroid gland of rats of the control pathology group, 1 month after the end of immunization with the human thyroid antigen in combination with a complete Adjuvant of Freund, the appearance of microscopic signs that are characteristic of autoimmune thyroiditis, primarily a kind of histological marker – Ashkenazi-Gürtle cells, was revealed. Cell proliferation, fibrous proliferation of stroma in the interlobular septa, the presence of small local lymphocytic infiltrates. All this occurs against the background of signs of hypotrophy, as evidenced by a decrease in the diameter of the follicles and an increase in the height of thyrocytes.

3 months after the end of immunization of rats with human thyroid antigen in combination with a complete Freund adjuvant, rats noted significantly more pronounced manifestations

of histological markers of autoimmune pathology of glandular tissue: proliferation of interlobular connective tissue layers was noted. The lobules distributed by fibrous cords are smaller. Focal lymphoid infiltration is more distinct (**Fig. 4**). The oxyphilic cell transformation of the epithelium also remains noticeable (**Fig. 5**). Increased manifestations of hypotrophy. The follicular epithelium showed signs of distinct proliferation. Papillary growths are more evenly expressed in different follicles, more often completely filling the entire follicle cavity.

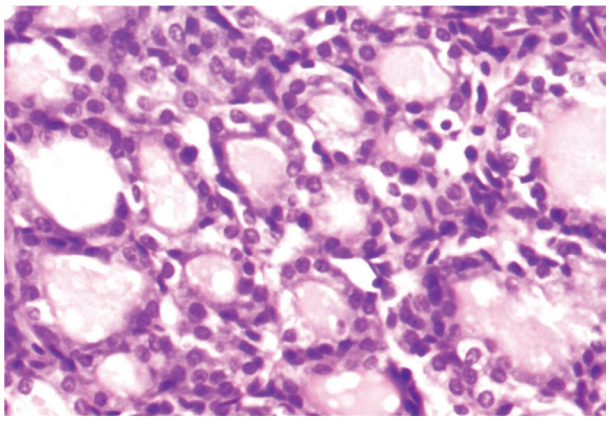

Fig. 3. Rat thyroid gland 1 month after the end of immunization with human thyroid antigen in combination with a complete Adjuvant of Freund. Ashkenazi-Gürtl cells are among typical thyrocytes. Hematoxylin-eosin, ×400

The follicles themselves are more equivalent in size, the proportion of microfollicles is relatively small. The contents of the colloid are small, often it is absent. Desquamation of thyrocytes is more pronounced. Only at the very periphery of the gland were noted a few follicles, in which the colloid was determined without obvious signs of proliferation of the epithelium (**Fig. 6**).

Morphometric measurements showed that the diameter of the follicles, as well as the height of the thyrocytes, practically remained stable (31–32 μm; 6.3 μm, respectively).

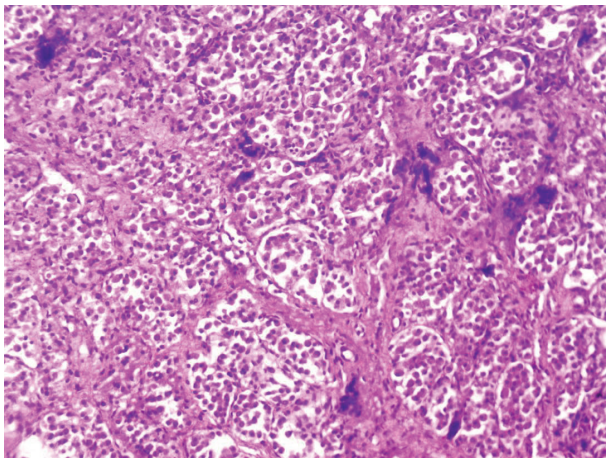

Fig. 4. Rat thyroid gland 3 months after the end of immunization with human thyroid antigen in combination with Freund's complete adjuvant. Expressive proliferation of the epithelium, desquamation of cells, absence of colloid, fibrosis of connective tissue layers, increased foci of lymphoid infiltration. Hematoxylin-eosin, ×200

6 months after the end of immunization with human thyroid antigen in combination with a complete Freund adjuvant in the microscopic picture of the glandular tissue parenchyma of a significant part of the rats, the severity of proliferation of the follicular epithelium was reduced,

microfollicles filled with liquid oxyphilic colloid or without it predominated. Areas were observed in which the lumen of the follicles was not determined, the epithelium was often disorganized, the pattern of tissue was lubricated. Signs of connective tissue proliferation and lymphocytic infiltration have progressed – wide fibrous fields infiltrated by lymphoid cells are visible **(Fig. 7)**.

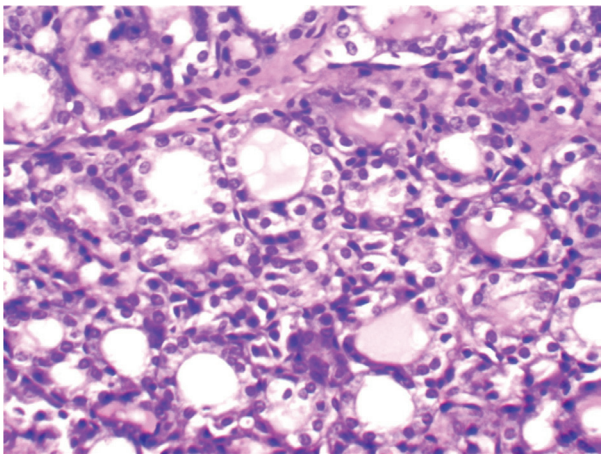

Fig. 5. Rat thyroid gland 3 months after the end of immunization of rats with human thyroid antigen in combination with Freind's complete adjuvant. Oxyphilic cell transformation of the follicular epithelium. The presence of follicles with complete replacement of thyrocytes with Ashkenazi-Gürtle cells. Hematoxylin-eosin, ×400

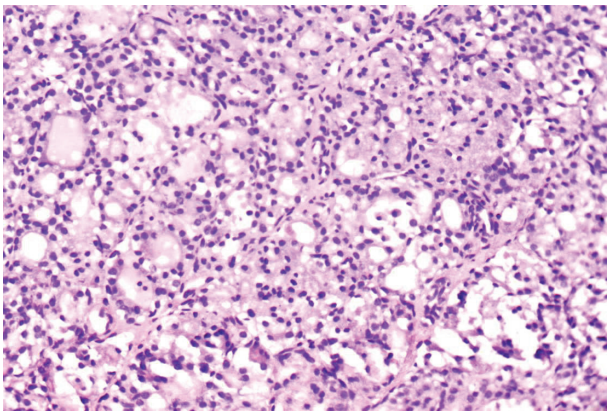

Fig. 6. Rat thyroid gland 6 months after the end of immunization of rats with human thyroid antigen in combination with Freind's complete adjuvant. The follicles are filled with liquid oxyphilic colloid or without it, the lumen of some follicles is not determined, the epithelium is disorganized. Hematoxylin-eosin, ×250

In these animals, the diameter of the follicles was 28 μm, the height of the thyrocytes increased to 8–18 μm, the number of cells in the wall reached 13 (if it is possible to assess these parameters). However, in a small proportion of animals, manifestations of regression were noted: the follicular type of the structure of the glandular parenchyma was much more preserved. The follicles were of different sizes, filled with colloid. Reduced signs of proliferation and lymphocytic infiltration, fibrosis. However, in several follicles, regardless of their size, the oxyphilic cell transformation of thyrocytes was preserved.

Morphometric indicators in these rats: the diameter of the follicles became 34 μm, the height of the cells – 5.9 μm, the number of cells in the wall decreased to 12.

Immunization caused the development of destructive-dystrophic disorders of the thyroid gland due to the humoral type of immune reactions and cytotoxic T cells, which led to the de-

struction of thyroid cells. Against the background of these degenerative changes in the gland, there was a decrease in its functional activity and general metabolic disorders, which was confirmed by hormonal, histological, immunological and biochemical studies.

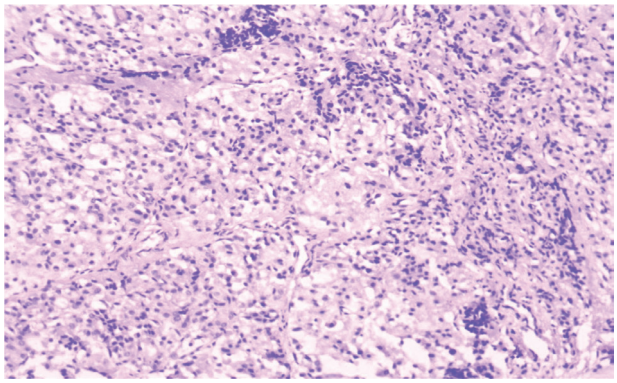

Fig. 7. Rat thyroid gland 6 months after the end of immunization of rats with human thyroid antigen in combination with Freund's complete adjuvant. The follicular type of tissue pattern is poorly distinguished, the epithelium is often disorganized, wide fibrous fields infiltrated by lymphoid cells are visible. Hematoxylin-eosin, ×200

One month after modeling, the histostructure of the parenchyma of the gland lost its follicular structure in many areas. The gland had a high density, an abnormal particle structure, and a bumpy surface. The weight of the gland increased.

Three months after modeling in the gland, there was a decrease in follicles, the disappearance of colloid in them, and the transformation of gland cells into epithelial strands of incorrect orientation.

Six months after the reproduction of autoimmune thyroiditis, the rats showed all the signs of the second, hypotrophic phase of this pathology, which was characterized by the destruction of the normal morphostructure of the thyroid parenchyma and persistent hypothyroidism. The study of the histostructure of the thyroid gland of experimental rats showed that the work reproduced a representative model of autoimmune thyroiditis with all the characteristic features – numerous foci of destruction of cellular elements of the parenchyma, the growth of connective tissue, the appearance of a large number of lymphoid infiltration fields of different sizes and locations.

It is planned to use this model for further study of the effect of biologically active compounds on the thyroid gland.

4. Conclusions

As a result of the simulation of autoimmune thyroiditis, we obtained an adequate response of the rat immune system to immunization with allogeneic antigen. A dynamic destructive change in the thyroid parenchyma was obtained, which was confirmed by morphological changes and secretory instability. There was an increase in atrophic changes, fibrosis, an increase in the number of oxyphilic cells (Gürtle cells), diffuse lymphoid infiltration. The process of autoimmune destruction, which was observed already a month after allogeneic immunization, intensified in the next 3 and 6 months. This model is quite stable and comparable to Hashimoto's autoimmune thyroiditis in humans. This model can be used to study new approaches to the treatment and prevention of autoimmune thyroid damage. The originality of this work also consists in the use of the postoperative human thyroid gland in rats as an antigen.

Conflict of Interest

The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining, and using its results, as well as any non-financial personal relationships.

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Data availability

Data will be made available on reasonable request.

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