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## RESULTS OF A MORPHOLOGICAL STUDY OF THE THYROID GLAND IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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The purpose of the study was to conduct a morphological analysis of autoimmune changes in the thyroid gland in patients with autoimmune thyroiditis who received various treatment methods. The work is based on 481 patients' treatment results, including surgical and diagnostic material. Using data from fine-needle aspiration puncture biopsy and cytological examination of punctate samples, the nature of cytological changes in the thyroid gland was assessed. The diffuse-nodular form of autoimmune thyroiditis is characterized in most patients by an autoimmune process with goiter changes manifested by nodular and multinodular encapsulated formations. Outside of goiter changes, atrophic and sclerotic changes in the parenchyma and stroma of the gland, lymphoplasmacytic infiltration and oxyphilic cell transformation of the follicular epithelium are detected. Smaller transitional forms of B cells are observed in the foci of oxiphilic cell transformation. In the diffuse-pseudonodular form of autoimmune thyroiditis, the described changes persist in most patients but with less frequency (54.7–68 %).

**Key words:** autoimmune thyroiditis, cytological changes, fine-needle aspiration biopsy

**Ф.Г. Садихов**

## РЕЗУЛЬТАТИ МОРФОЛОГІЧНОГО ДОСЛІДЖЕННЯ ЩИТОВИДНОЇ ЗАЛІЗИ У ХВОРИХ НА АУТОІМУННИЙ ТИРЕОЇДИТ

Метою дослідження було проведення морфологічного дослідження аутоімунних змін щитовидної залози у хворих на аутоімунний тиреоїдит, які отримували різні види методів лікування. Робота ґрунтується на вивченні результатів лікування 481 хворого. Досліджено операційний та діагностичний матеріал, отриманий від пацієнтів із різними формами аутоімунного тиреоїдиту. На підставі даних тонкоголкової аспіраційної біопсії та цитологічного дослідження пунктати (за системою Bethesda) проведено оцінку характеру цитологічних змін щитовидної залози у хворих, які перенесли різні методи лікування. Вузлова форма аутоімунного тиреоїдиту у більшості хворих характеризується ознаками аутоімунного процесу у поєднанні із зобними змінами, які проявляються вузловими та багатовузловими інкапсульованими утвореннями. Мають переважно колоїдну будову. Поза зобними змінами виявляються атрофічні та склеротичні зміни паренхіми та строми залози, лімфоплазмоцитарна інфільтрація та оксифільноклітинна трансформація фолікулярного епітелію. У вогнищах окисифільноклітинної трансформації спостерігаються дрібніші перехідні форми В-клітин. При дифузно-хибновузловій формі аутоімунного тиреоїдиту описані зміни зберігаються у більшості пацієнтів, але зустрічаються вони з меншою частотою (від 54,7 до 68 %).

**Ключові слова:** аутоімунний тиреоїдит, цитологічні зміни, тонкоголкова аспіраційна біопсія.

According to the literature, the frequency of autoimmune thyroiditis (AIT) among all thyroid diseases is 25–35 %, ranking it second after diabetes among endocrinological diseases. Autoimmune thyroiditis primarily affects women aged 35–65 years [8, 13]. The issues of choosing a treatment method for patients with AIT are still far from a final decision. Despite reasonable indications for surgical treatment of nodular forms of AIT, the choice of treatment for patients with a diffuse form of the disease remains

open. The diffuse form of AIT occurs in approximately 40–60 % of patients [5, 7]. The clinical picture of the disease is determined by the severity and prevalence of pathological changes in the thyroid gland. An important pathomorphological criterion of autoimmune thyroiditis is the oxyphilic transformation of the follicular epithelium. Oxyphilic transformation is characterized by the appearance in the thyroid gland of B-cells, which line the follicles of the gland or form solid accumulations. The final feature of these cells is the eosinophilic granularity of the cytoplasm and a negative reaction to thyroglobulin. In the morphometric study of B-cells, their height sharply increases [1, 12].

According to the morphological study, the following characteristic features of this form of AIT are revealed: atrophy of the parenchyma of the gland, a decrease in the diameter of the follicles by more than five times, flattening of the follicular epithelium, a decrease in the height of the thyroid epithelium by half and lymphoid infiltration of the stroma with the formation of lymphatic follicles, oxyphilic transformation of the follicular epithelium [2, 6].

In most cases, fine-needle aspiration puncture biopsy (FNAB) with cytological examination using the Bethesda system makes it possible to determine the nature of the nodule [3, 9]. However, it is not always possible to verify the diagnosis of AIT by cytological signs. Sometimes thyrocytes of benign follicular neoplasias are morphologically indistinguishable from follicular carcinoma cells [10, 11]. The same facts significantly complicate the identification of pathological changes in cells in autoimmune thyroiditis. Sometimes the term “follicular tumor” unites all nodular formations in the thyroid gland, including those formed against the background of AIT [3, 15]. In practice, a benign tumor such as follicular or microfollicular adenoma is often found in combination with autoimmune thyroiditis. Hence, improving the sensitivity and specificity of diagnostic methods for AIT is important for determining appropriate treatment strategies for these patients [4, 14].

In this regard, the problem arises not only of timely and accurate diagnosis of the disease but also of a clear prognosis during the course of the disease, which is very important in choosing the optimal treatment option for AIT for each patient. Despite research into the main pathogenetic mechanisms, the diagnostic criteria and morphological changes associated with AIT are still not clear enough.

**The purpose** of the study was to conduct a morphological analysis of autoimmune changes in the thyroid gland in patients with autoimmune thyroiditis who received various treatment methods.

**Materials and methods.** The work is based on the study of the treatment results of 481 patients hospitalized at the clinical base of the Scientific Center of Surgery named after Academician M.A. Topchubashov. The surgical and diagnostic material obtained from patients with various forms of autoimmune thyroiditis, who received different treatment methods, was studied. A total of 207 thyroid preparations from the years 2008 to 2022 were studied. In 4 (1.9 %) of 207 patients, the diagnosis of B-cell adenoma was histologically verified. The remaining observations were preparations of patients with autoimmune thyroiditis. There were 26 (12.6 %) males, 181 (87.4 %) females. The nature of cytological changes in the thyroid gland was assessed based on fine-needle aspiration puncture biopsy (FNAB) and cytological examination using the Bethesda system for patients who underwent various treatment methods.

Out of 481 patients treated in the clinic, we identified three groups of patients, taking into account the treatment methods used. The first group included 129 (29.2 %) patients who received a course of conservative therapy in combination with sessions of intravenous laser blood irradiation with low-intensity laser radiation (ILBI-LILR). The “Solaris” apparatus was used for intravenous laser blood irradiation. 103 (79.8 %) patients were followed up during the follow-up period from 1 to 5 years. For replacement therapy, levothyroxine preparations were prescribed approximately at the rate of 1.7 μg/kg/day of the patient's body weight.

The second group included 106 (24.0 %) patients who were treated with laser photodynamic therapy (PDT) and ILBI-LILR sessions. 80 (75.5 %) out of 106 patients in this group were followed up for 3–5 years inclusive. For laser photodynamic therapy, the phototherapeutic apparatus AFS “Harmony” was used. The third group consisted of 207 (46.8 %) patients who underwent surgery for a complicated form of AIT. In the postoperative period, 96 patients of this group received 7–8 courses of ILBI-LILR. Among the patients of the third group, we tracked the long-term results of 157 (77.7 %) of 207 patients for 3–5 years after surgery.

All suspicious areas were marked, and pieces were taken from them for histological examination. The pieces were fixed in a 10 % neutral buffered formalin solution, passed through alcohols of increasing strength, and embedded in paraffin. Sections measuring 5–6 microns thick were prepared from the paraffin blocks. Histological examination was carried out according to the standard method on paraffin sections stained with hematoxylin and eosin, picrofuchsin according to Van Gieson, and toluidine blue**.** To identify the colloid, the PAS reaction was used according to the semi-quantitative method of A.L. Shabadash; the

result was evaluated by the intensity of colloid staining, as a weakly positive, moderate, and pronounced reaction. An urgent histological examination of thyroid nodules and regional lymph nodes was also performed according to the standard method based on obtaining frozen sections without fixation, stained with hematoxylin.

In each group, the mean values of the analyzed clinical indicators and the significance of intergroup differences were calculated according to the Pearson $\chi^2$, Mann – Whitney U, and Student – T tests. Differences were considered statistically significant at $p<0.050$.

**Results of the study and their discussion.** We analyzed the data of the morphological study. The most characteristic morphological sign of AIT is lymphoplasmacytic infiltration of the stroma of the gland. The composition of cells is always constant; it combines cells of the lymphoid series, plasmacytic infiltration, and macrophages. Plasmacytic infiltration is diffuse and, as a rule, prevails over lymphoid. The degree of lymphoplasmacytic infiltration can vary, both among different glands and within different regions of the same gland. During a general examination of the preparations, the thyroid tissue of patients with AIT has a characteristic appearance: against a dark background of dense lymphoplasmacytic infiltration, small follicles, strands, and individual cells of a large light oxyphilic epithelium (Gurtle cells) are clearly distinguished. The presence of these cells is a typical sign of AIT. The appearance of these cells is very characteristic. They are 3–4 times larger than usual and have a wide oxyphilic granular cytoplasm. These cells often possess enlarged nuclei, which can give the false impression of tumor growth due to variations in cell size, hyperchromatosis, and nuclear polymorphism.

In some parts of the gland, among the plasmacytic infiltration, regenerative growth of the epithelium can be observed; small islands of light cells with microfollicles and layers of basophilic cells without the formation of follicles with many mitoses.

The diffuse nodular form of AIT in most patients is characterized by signs of an autoimmune process in combination with goiter changes, which are manifested by nodular and multi-nodular encapsulated formations. They have a mostly colloidal structure. Outside goiter changes, atrophic and sclerotic changes in the parenchyma and stroma of the gland, lymphoplasmacytic infiltration and oxyphilic cell transformation of the follicular epithelium are detected. But compared with atrophic or diffuse, lymphoplasmacytic infiltration is less common and less pronounced. Smaller transitional forms of B-cells are observed in the foci of oxidative cell transformation. In the diffuse-pseudonodular form of AIT, the described changes persist in most patients, but they occur less frequently.

The diffuse form of AIT is characterized by severe deformation and atrophy of the lobules, ingrowth of bundles of connective tissue into the lobules of the gland in the form of strands with the formation of reticular sclerosis. There is no oxyphilic cell transformation of the epithelium. Focal lymphocytes are mainly represented by T-lymphocytes. Lymphocytic infiltrates are small. The atrophic form of AIT is characterized by pronounced atrophic changes in the parenchyma of the gland, activation of desmoplastic processes with diffuse sclerotic changes in the stroma, oxyphilic cell transformation of the thyroid epithelium, and lymphoplasmic cell infiltration.

We used the classification of Polyakova AV. (1997) in which the author identifies three main degrees of morphological changes in this disease (Table 1).

Table 1

**Frequency of morphological changes in patients with various forms of thyroiditis**

| Forms of thyroiditis | Degree of morphological changes | | | All patients |
|---|---|---|---|---|
| | I | II | III | |
| Hypertrophic: n=257 | | | | |
| – Diffuse n=76 | 20 (26.3 %) | 31 (40.8 %) | 25 (32.9 %) | 76 (15.6 %) |
| – Dif.-pseudonodular n=75 | 15 (20.0 %) | 19 (25.3 %) | 41 (54.6 %) | 75 (15.6 %) |
| – Diffuse-nodular n=106 | 30 (28.3 %) | 19 (17.9 %) | 57 (53.8 %) | 106 (22.0 %) |
| Atrophic n=63 | 19 (30.1 %) | 19 (30.1 %) | 25 (39.7 %) | 63 (13.1 %) |
| Recurrent n=46 | 5 (10.9 %) | 10 (21.7 %) | 31(67.4 %) | 46 (9.6 %) |
| Thyrotoxic n=76 | 34 (44.7 %) | 25 (32.9 %) | 17(22.4 %) | 76 (15.6 %) |
| Thyroid cancer n=39 | 11 (28.2 %) | 13 (25.6 %) | 15(38.5 %) | 39 (8.1 %) |
| Total | 134 (27.3 %) | 136 (28.3 %) | 211 (43.9 %) | 481 (100 %) |

In diffuse and diffuse-pseudonodular hypertrophic forms of autoimmune thyroiditis, there is no statistical difference between grades I and II of morphological changes of the thyroid gland ($\chi^2_{emp}=0.20$, $p>0.05$), and a statistical difference is noted between grades II and III ($\chi^2_{emp}=6.70$, $p<0.01$), a statistically significant difference is observed between I and III degrees ($\chi^2_{emp}=3.39$, $p<0.05$).

During the diffuse-pseudonodular and diffuse-nodular hypertrophic forms, there is no statistical difference between degrees I and II of the morphological changes of the thyroid gland ($\chi^2_{emp}=2.32$, $p>0.05$),

II and III degrees ($\chi^2_{emp}$=0.73, p>0.05), there is no statistical difference between grades I and III ($\chi^2_{emp}$=0.94, p>0.05).

In diffuse and diffuse-nodular forms, there is no statistical difference between degrees I and II of the morphological changes of the thyroid gland (p>0.05), their indicators are close to each other, a statistical difference is recorded between degrees II and III ($\chi^2_{emp}$=12.6, p<0.005), and no statistical difference is observed between grades I and III ($\chi^2_{emp}$ =1.32, p>0.05).

In the hypertrophic and atrophic forms of autoimmune thyroiditis, there is no statistical difference between grades I and II of morphological changes of the thyroid gland (p>0.05), as well as grades II and III ($\chi^2_{emp}$=0.80, p>0.05), grades I and III no statistical difference was recorded between them ($\chi^2_{emp}$=1.15, p>0.05). No statistical difference was recorded between degrees I and II of the morphological changes of the thyroid gland in the forms of recurrent goiter and thyrotoxic ($\chi^2_{emp}$=2.9, p>0.05), II and III degrees ($\chi^2_{emp}$=10.39, p<0.005). A statistically significant difference is recorded between grades I and III ($\chi^2_{emp}$=23.78, p<0.002). There is no statistical difference between grades I, II, and III of morphological changes of the thyroid gland in hypertrophic and thyroid gland cancer forms of AIT ($\chi^2_{emp}$=1.26, p>0.05).

In the diffuse-nodular form of thyroiditis, lymphoplasmacytic infiltration and changes in the epithelium occupy small areas in the gland tissue. Small foci are lymphoid infiltrates and lymphoid follicles with reproduction centers. In large foci, an attached plasmacytic infiltration of the surrounding tissue can be detected.

In the atrophic form of AIT, stromal sclerosis increases, leading to the disappearance of plasma cells, while lymphoid infiltration persists in the form of small foci. Changes in fibrous structures are permanent. At the same time, interlobular connective tissue layers grow in the stroma of the gland, and thus powerful fibrous cords are formed that separate the lobules of the gland into smaller sections.

The data presented in Table 1 allow us to note that the most frequently pronounced cytological changes were detected in the hypertrophic form of AIT (more precisely in diffuse-nodular–53.8 % of cases and in diffuse-pseudonodular forms (54.6 %)). More than 2/3 of observations (67.4 %) showed severe cytological changes in patients with recurrent thyroiditis in patients with AIT. Among patients with a diffuse form of AIT (in 56 (73.7 %) out of 76 (15.6 %) people), less pronounced changes (I–II degrees) are noted.

Thus, most often, the most pronounced cytological changes were detected in diffuse nodular and diffuse-pseudonodular forms (in 53.8 % and 54.6 % of patients) of thyroiditis. Our studies give reason to believe that such morphological changes can be considered irreversible, and they are unlikely to undergo regression under the influence of conservative therapy. Therefore, we interpreted such a course of the disease as complicated and considered such clinical and morphological changes in AIT as an indication for surgical treatment of the patient. Further observation of such patients showed that the disease progressed over time, sometimes quite quickly (pronounced local changes developed). The patients clearly showed a tendency of growth and enlargement of the thyroid gland with the formation of a large goiter (in 46 (16.3 %) of 283 people (IV–V degree).

During a pathohistological examination of preparations for the purpose of a deeper analysis of structural changes in the thyroid gland, taking into account the form of autoimmune thyroiditis in patients, we examined the most common morphological changes (Table 2).

In diffuse, diffuse-nodular, and diffuse-pseudonodular forms of autoimmune thyroiditis, there is no statistical difference between the indicators of atrophic changes in the parenchyma of the gland and diffuse sclerotic changes in the stroma ($\chi^2_{emp}$=3.10, p>0.05); a statistically high difference is observed between cases of enlargement, deformation, and formation of the gland (p<0.0001); no statistical difference is recorded between cases of epithelial proliferation against the background of a nodule with an undefined capsule and atrophic and sclerotic changes ($\chi^2_{emp}$=2.61, p>0.05).

In diffuse-pseudonodular and atrophic forms, activation of desmoplastic processes, transformation of thyroid gland epithelium into oxyphil cells, lymphoplasmacytic infiltration of B-cell groups, the formation of follicles, and the cases of total accumulation of cells are recorded ($\chi^2_{emp}$=9.07, p<0.001).

A statistical difference was recorded between the growth, deformation, and formation of the gland during the recurrent goiter and thyrotoxic forms of autoimmune thyroiditis, the activation of desmoplastic processes, and the occurrence of diffuse sclerotic changes in the stroma ($\chi^2_{emp}$=4.08, p<0.05). In those forms of autoimmune thyroiditis, there is also a statistical difference between the transformation of the thyroid epithelium into oxyphil cells and lymphoplasmacytic infiltration, the formation of B-cell groups and follicles, and the total accumulation of cells, the nodule with an undefined capsule, and the proliferation of the epithelium against the background of atrophic, sclerotic changes ($\chi^2_{emp}$=7.62, p<0.01).

Table 2

**The frequency of structural changes in the thyroid gland in patients with various forms of AIT (absolute and in %)**

| Form of AIT | Atrophic changes in the parenchyma of the gland | The gland is enlarged and deformed, there is a goiter | Activation of desmo plastic processes | Diffuse sclerotic changes in the stroma | Oxyphilic cell transformation of the thyroid epithelium and lymphoplasmacytic infiltration of B-cell accumulation. Solid aggregations of cells with follicle formation | The presence of a node with an indistinct capsule | Proliferation of the epithelium against the background of atrophic and sclerotic changes |
|---|---|---|---|---|---|---|---|
| Diffuse n=76 | 3 (3.9 %) | 7 (9.2 %) | 23 (30.3 %) | 21 (27.6 %) | | 14 (18.4 %) | 17 (22.4 %) |
| Diffuse–nodular n=106 | 4 (3.8 %) | 102 (96.2 %) | | 17 (16.0 %) | 104 (98.1 %) | 45 (42.4 %) | 103 (97.2 %) |
| Diffuse–pseudonodul. n=75 | 5 (6.7 %) | 51 (68.0 %) | 14 (18.7 %) | 9 (12.0 %) | 41 (54.7 %) | 23 (30.7 %) | 49 (65.3 %) |
| Atrophic n=63 | 63 (100 %) | | 62 (100 %) | 63 (100 %) | 63 (100 %) | 63 (100 %) | 49 (77.8 %) |
| Recurrent n=46 | | 46 (100 %) | 4 (8.7 %) | 11 (23.9 %) | 46 (100 %) | 46 (100 %) | 46 (100 %) |
| Thyrotoxic n=76 | | 76 (100 %) | 9 (11.8 %) | 7 (9.2 %) | 57 (75.0 %) | 34 (44.7 %) | 76 (100 %) |

Therefore, in most patients, the diffuse-nodular form of AIT is characterized by signs of an autoimmune process in combination with goiter changes, which are manifested by nodular and multinodular encapsulated formations. They have a mostly colloidal structure. Outside goiter changes, atrophic and sclerotic changes in the parenchyma and stroma of the gland, lymphoplasmacytic infiltration and oxyphilic cell transformation of the follicular epithelium are detected. But compared with atrophic, diffuse lymphoplasmacytic infiltration is less common and less pronounced. Smaller transitional forms of B-cells are observed in the foci of oxidative cell transformation. In the diffuse-pseudonodular form of AIT, the described changes persist in most patients, but they occur with a lower frequency (from 54.7 % to 68.0 %).

The diffuse form of AIT is characterized by severe deformation and atrophy of the lobules, ingrowth of bundles of connective tissue into the lobules of the gland in the form of strands with the formation of reticular sclerosis. There is no oxyphilic cell transformation of the epithelium. Focal lymphocytes are mainly represented by T-lymphocytes. Lymphocytic infiltrates are small.

The atrophic form of AIT is characterized by pronounced atrophic changes in the parenchyma of the gland, activation of desmoplastic processes with diffuse sclerotic changes in the stroma, oxyphilic cell transformation of the thyroid epithelium, and lymphoplasmic cell infiltration. In addition, the disease is manifested clinically by the development of overt hypothyroidism. We observed a similar course of the disease in 68.2 % of patients with the diffuse-nodular form of AIT. In patients with diffuse and atrophic forms of AIT, the clinical picture of the disease differs from that described. Complications in the form of goiter formation are rare, but hypothyroidism develops in these patients quite often. In our studies, such a course of the disease was detected in 20.3 % of cases.

According to the literature, the natural course of AIT in patients is characterized by progression from latent and subclinical stages to clinical and is associated with the presence of specific circulating autoantibodies [2]. In contrast to published works, our study examined morphological changes in the thyroid gland in patients diagnosed with autoimmune thyroiditis who received various types of treatment methods. Limitations in the study include the lack of a unified protocol dedicated to the problem of morphological diagnosis of AIT. Despite the widespread prevalence of autoimmune thyroiditis and the long history of conservative therapy, the effectiveness of adequate treatment of AIT is still relevant today. The disadvantage of existing known drug therapies is their low effectiveness, as well as the possibility of complications and relapses of the disease [6, 11].

Concluding the study, we can firmly state that the use of laser technologies can guarantee the best results in the treatment of patients with diffuse autoimmune thyroiditis. Having a pronounced local effect on the cellular and tissue structure of the thyroid gland, the combined use of laser radiation can provide a beneficial effect and a positive outcome in the treatment of the disease [4, 13].

## Conclusion

Analysis of the data of clinical, instrumental, laboratory, and morphological studies discussed in this article suggests that patients with diffuse-nodular and diffuse-pseudonodal forms of AIT often have a complicated course of the disease. For these forms, the characteristic features are the growth and enlargement of the thyroid gland. The progression of the disease leads to changes in the structure of the thyroid gland in which goiter changes occur (multiple foci of lymphoid and plasmacytic infiltration are formed), and goiter (nodular or multinodular) is formed locally.

Conservative (replacement) therapy based on the principle of taking levothyroxine in combination with sessions of ILBI-LILR occupies an important place in the arsenal of available methods for the treatment of patients with AIT. There is reason to recommend this method for use in patients with the atrophic form of AIT, in women with postpartum thyroiditis, and is also indicated as maintenance therapy in patients with hypothyroidism after surgery. The euthyroid state is achieved by prescribing replacement therapy with levothyroxine at a daily dose of 50 $\mu$g/kg per day.

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