Characteristics of Riedel’s and Hashimoto thyroiditis based with morphological and immunohistochemical data

Accepted 14th March 2019

ABSTRACT

Riedel’s thyroiditis is a rare, chronic inflammatory disease of the thyroid gland characterized by a dense fibrosis that replaces normal thyroid parenchyma. The etiology is unknown, one theory of pathogenesis postulates that this is results from an autoimmune process. A second theory holds Riedel’s thyroiditis to be a primary fibrotic disorder. We studied the tissue samples of the thyroid gland received by 62 patients in operation: Hashimoto’s thyroiditis (n = 27), Riedel’s thyroiditis (n = 8), Graves’ autoimmune disease (n = 17), and Papillary Thyroid Carcinoma (n = 10). Based on the results obtained, we can conclude: histological and immunohistochemical heterogeneity is characteristic for autoimmune thyroiditis, but for both processes (Hashimoto’s thyroiditis, Riedel’s thyroiditis) it is specific to the progressive introduction of glandular tissue and replacement with rigid, sometimes scar tissue. According to molecular-biological research data, we can not exclude dysplatic and neoplastic transformation in progenitor cells during Hashimoto’s thyroiditis versus Riedel’s autoimmune Thyroiditis.

Key words: Riedel’s thyroiditis, hashimoto thyroiditis, histology, immunohistochemistry.

Abbreviations: RT, Riedel’s thyroiditis; HT, Hashimoto thyroiditis; PTC, papillary thyroid carcinoma.

INTRODUCTION

Riedel’s thyroiditis (RT) is a rare, chronic inflammatory disease of the thyroid gland characterized by a dense fibrosis that replaces normal thyroid parenchyma (Riedel, 1896). The fibrotic process invades adjacent structures of the neck and extends beyond the thyroid capsule. This feature differentiates RT from other inflammatory or fibrotic disorders of the thyroid. Extension beyond the thyroid also differentiates this from the fibrous variant of Hashimoto thyroiditis (Guerin, 2017).

Involvement in RT may be unilateral or bilobar. Thyroid function depends on the extent to which the normal thyroid gland has been replaced by fibrotic tissue. Most patients are euthyroid, but hypothyroidism is noted in approximately 30% of cases. Rarely, hyperthyroidism can occur, but this is probably secondary to a coexisting condition (Schwaegerle et al., 1988).

The etiology of RT is unknown, but it may be related to a relatively new group of rare disorders, IgG4-related systemic disease (IgG4-RSD) (Li et al., 2012; Katabathina et al., 2016). One theory of pathogenesis postulates that RT results from an autoimmune process. A second theory holds RT to be a primary fibrotic disorder (Pusztazeri et al., 2012). However, IgG4-RSD may unify these 2 seemingly disparate etiologies.

The following evidence supports an autoimmune pathogenesis for RT (Takeshima et al., 2015; Dahlgren et al., 2010):

• The presence of antithyroid antibodies in a significant
percentage of patients with RT (67%):
• The pathologic features of cellular infiltration, including lymphocytes, plasma cells, and histiocytes;
• The frequent presence of focal vasculitis on pathologic examination;
• The favorable response of a subset of patients with RT to treatment with systemic corticosteroids.

The theory that RT is a primary fibrotic disorder is supported by its association with multifocal fibrosclerosis. This uncommon idiopathic syndrome is characterized by fibrosis involving multiple organ systems. The extracervical manifestations of multifocal fibrosclerosis can include retroperitoneal fibrosis, mediastinal fibrosis, orbital pseudotumor, pulmonary fibrosis, sclerosing cholangitis, lacrimal gland fibrosis, and fibrous parotitis (Fatourechi et al., 2011). RT may be 1 manifestation of this multifocal disease (Levy et al., 2010; Soh et al., 2013).

The histopathologic changes of RT closely resemble those observed in multifocal fibrosclerosis. Additionally, one third of published RT cases have demonstrated at least 1 manifestation of extracervical fibrosclerosis. The ability of systemic corticosteroids and tamoxifen to inhibit fibrogenesis accounts for the favorable effect of such treatment in both conditions (Lee et al., 2013; Elizabeth et al., 2003).

MATERIALS AND METHODS

Patients

The research database is a comprehensive treatment for total thyroiditis from both sexes, operational material obtained after total thyroidectomy, unilateral lobectomy and partial resection of the thyroid gland. Retrospective material was used. All clinical diagnostic data were collected. All patients provided written informed consent.

From the 27 cases of Hashimoto’s, 21 cases have been inherited by the Hashimoto goiter of any size or thyroiditis. There was no hereditary load during the Riedel’s thyroiditis.

For the purpose of evaluating the data, the study included 17 cases of Graves’ disease, in which case 6 cases of inheritance were reported in the case of different thyroid pathologies (hypo- and hyperthyroidism, pregnancy dysfunction) and 10 cases of Papillary Thyroid Carcinoma (PTC) were used as control group (Jankovic et al., 2013; Cipolla et al., 2005). The total number of patients was 62.

Sex

1. Hashimoto’s thyroiditis (HT) (n = 27, female -20, male - 7)
2. Riedel’s thyroiditis (n = 8, female -8, male - 0)
3. Graves’ autoimmune disease (n = 17, female -12, male - 5)
4. PTC (n = 10, female - 10, male - 0)

Age

The age of the patients varied from 25 to 76 years, the average age was 50 ± 5 years.

Clinical manifestation

The most common symptoms of RT are the local compressive symptoms: dysphagia, dyspnea, sore throat and cough. Hypothyroidism was reported in 30% of cases. According to the literary data, fibrosis of nearby anatomical structures can rarely cause recurrence symptoms of laryngeal nervous paralysis or hypoparathyroidism, which has not been established on our material.

Hashimoto’s most common symptoms include thyroid labor, easily tiredness, weight gain, thermal rejection, joint and muscle pains, bradycardia, dysmenorrhea, and other types of reproductive dysfunction.

The symptoms of Graves’s disease are caused by direct and indirect effects of hyperthyroidism. Our material has been dysfunctional of CNS dysfunction, more frequently; signs of excitation, as well as tolerance to temperature, decreased weight in the face of increased appetite, especially remarkable are the muscle weakness, various forms of heart rhythm and conductivity.

Histological and immunohistochemical (IHC) methods of study

The material is the tissue samples of the thyroid gland in the operative path. 75% of patients were treated with lobectomy, totally or partial thyroidectomy. Material received Surgical Card of Tbilisi Clinics and National Center for Interventional Medicine of West Georgia, it is represented as retrospective (2014-16 years), as well as analysis of prospecting research (2017-18 years).

Tissue samples of thyroid gland obtained by operated 10% of the formalized buffer solution were then painted with H&E. After the selection, the material was prepared for immunohistochemical research.

Based on the main task of research, tissue samples were studied using the following antibodies:

1. Thyroid transcription factor 1 (TTF1) (clone SPT24, Novocastra)
2. Protein S100 (RTU-S100p Polyclone Antibodies) (Biogenex)
3. CD34 (clone QBEnd / 10, Novocastra)
4. TSH (Biogenex)
5. CD56 (clone, CD564, Leica, UK)
6. p63 (clone 7JUL, Leica, UK).

Each marker was evaluated in 500-100 cells of 8-10 patients of individual groups.

Sections were fixed on poly-L-lysine-coated glass slides and prepared as follows: 1) deparaffinization, rehydration and incubation for 20 min in 3% H$_2$O$_2$; 2) Immersion in phosphate-buffered saline (PBS) for 20 min; 3) Antigen retrieval in the microwave (600 W) for 20 min, followed by cooling in citrate buffer (0.01 m, pH 6.0).

Specimens were incubated with the primary antibodies for 1 hour at room temperature. Then was washed three times with PBS at room temperature. Hematoxyline is used to power the nuclei.

All procedures were carried out in compliance with antibodies manufacturer's protocols (BioGenex, USA; Novocastra, UK).

Statistc analysis

The statistic analysis was performed using Microsoft Excel 7.0, SPSS-22 version and Mann – Whitney U – test (p value <5%).

RESULTS AND DISCUSSION

Results of histopathological research of Hashimoto's thyroiditis and activity of parallel immunohistochemical reactions indicate that the thyroid parenchyma is non-homogeneous in terms of cell components, as well as molecular biological features.

Hashimoto's thyroiditis leading histopathological process is the introduction of thyroid parenchyma (Figure 1), which is accompanied by hypertrophy/hyperplasia of lymphoid follicular and secondary germination centers, with the abundance of macrophages and plasma cells. In the thyroid, parenchyma atrophic follicles and necrosis areas were detected. The atrophic-invasive process of parenchyma confirms the negative reaction in the lymphoid tissue and the diffuse-focal expression of the same marker in isolated tissues of the gland with CD34 (precedent growth factor).

In Riedel's thyroiditis, both histological and immunohistochemical characteristics of thyroid gland revealed active transformational and fibroplastic processes in the gland parenchyma, namely: diffuse-focal moderate expression of TTF-1 in stroma fibroblasts and capillary endotheliocytes. The TTF-1 positive structures were revealed in stromal elements and in the surrounding areas of the capillary wall in the form of clusters and combined bales.

In Riedel's thyroiditis, there is a deliberate replacement of glandular parenchyma with connective graft and reduction of the production of the thyroid hormone cellular mass. It is noteworthy that the activation of the neuroectodermal genesis cells (Hurtle Cells) does not change, as evidenced by the diffuse-mixed expression of the specific S100 protein in the parafollicular domains.

Graves' disease - characteristic of the control group material, is undergoing a TSH-dependent hyperplasia of follicular cells, showing clinical picture of hyperthyroidism and does not contain immuno- and cellular potential of malignancy (Rurua et al., 2015).

Due to the interest of our research, in the case of the main and control group, tissue samples were studied in CD56 and p63 receptor activity. CD56, except that the nerve cell adhesion molecule, is expressed in the normal, non-neoplastic thyroid follicular cells and its expression decreases the thyroid neoplasm, especially in the PTC (Harb, 2017). In Hashimoto's "parenchyma" PTC, progressive detection of the precursor cells and their markers, as well as the presence of high intensity lymphocytic infiltration as the immunological factor of progression of malignancy, were expressed (Gogiashvili et al., 2017).

We suggest that the biomarkers CD56 and p63 could be used to detect a normal, non-neoplastic follicular cell. Moreover, it is described in the case of malignisation CD56 expression, which indicates the final malignant transformation of follicular cells (Rasha and Lobna, 2012). On the other hand, the expression of tumor protein p63 (TP63) – as member of the p53 transcription factors and stem/progenitor cell regulator, also may be considered as sensitive predictive factor of malignancy. Finally, both of these ideas are based on previous researches (Rurua et al., 2015; Gogiashvili et al., 2017).

Comparative study of the Riedel's and Hashimoto's thyroiditis has shown the following results: during Hashimoto's thyroiditis CD56, negative or weak positive reaction was observed, indicating the presence of malignant potential in the tested case (Figure 2a).

As seen from the material, the p63 does not give a significant reaction to the PTC, while the CD56 adhesive factor shows a high expression in the colloid and in fact a significant reaction to the PTC, while the CD56 adhesive receptor response to glandular cells.

In case of papillary carcinoma (Figure 2), CD56 receptor-positive area is only found in the colloid.

In case of papillary carcinoma (as positive control) tumor tissue reaction in p63 protein was negative and moderately positive to the apoptotic cells nuclei (Figure 3b).

In the case of Riedel's thyroiditis, the active fibroplastic transformation of the thyroid gland parenchyma was observed in a weak baseline reaction of p63 (Figure 3a). It can be assumed that in the Riedel's thyroiditis, case p63 protein, as the "cancer stem cells" molecular structure, does not appear in the glandular tissue with that approach in mind that malignisation potential, the abovementioned type of autoimmune thyroiditis, is minimal.
Figure 1: H&E, X100. a. HT-the reduction of thyroid parenchyma (1), lymphoid nodules hypertrophy with fused secondary germinative centers (2). b. RT-small follicular structures, severe fibrosis(1).

Figure 2: CD56 expression, immunoperoxidase reaction, X100. a. HT-weak reaction. b. RT-high positive diffuse reaction in the colloid, negative expression in follicle cells (1). c. PTC- marked expression in the colloid (1), negative- in glandular tissue (2).

Thus, CD56 expression in the Riedel’s thyroiditis parenchyma was not observed in the follicular cells, only in the colloid, like the papillary carcinoma (Figure 2b), and was unequally negative as Hashimoto’s thyroiditis both glandular and stromal structures. According to previous studies on observation data about CD56 predicting role in
**Table 1**: Immunohistochemical markers activities in the compared groups (HT, RT).

<table>
<thead>
<tr>
<th></th>
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<th>Mann-Whitney U-Test</th>
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<td>CD56</td>
<td>10</td>
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*: The correlation is significant at the level 0.05.

**Table 2**: Immunohistochemical markers activities in the compared groups (Hashimoto, PTC).

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**Table 3**: Immunohistochemical markers activities in the compared groups (RT, PTC).

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**Figure 3**: p63 expression, immunoperoxidase reaction. a. RT- weakly background reaction, X100. b. PTC-apoptotic nuclei (arrow) moderately positive, X400.
Figure 4: Chart of average of IHC in the compared groups.

Figure 5: Chart of average of IHC in the compared groups.

Figure 6: Chart of average of IHC in the compared groups.
Hashimoto's Thyroiditis (considering malignisation potential), this marker was also used for differentiating between HT and RT risk as PTC precursors. There is important significant positive correlation in CD56 and p63 activities and PTC developing within HT parenchyma, on one hand, and absence of specific link in CD56 activity and neoplastic transformation possibility into RT, on the other hand (Mann-Whitney U-Test, respectively) (Table 1).

Conclusion

As mentioned above, Hashimoto's thyroiditis is characterized by lymphoplasmocytic infiltration, associated with massive invasion in the parenchyma. Fibroplastic processes in Riedel's thyroiditis occur in the form of acellular fibrosis, which is accompanied by a follicular reduction, similar to Hashimoto's thyroiditis dynamics, but our study result involving the examination of the papillary carcinoma and its immuno-profile showed the following: during the PTC, there was typically a high CD56 activity, which was confirmed by high correlation using Mann-Whitney U-Test (Tables 2, 3).

In contrast, Riedel's thyroiditis was presented in negative receptors for CD56 and p63 in glandular cells. Due to the biopotential of these two factors, Riedel's thyroiditis disorders, despite to Hashimoto thyroiditis, have low malignisation potential and consequently, the cancer stem/progenitor does not exist in the cellular population, as well as the results of TTF1 research (Figures 4 to 6).

Based on all the data, we can conclude: histological and immunohistochemical heterogeneity is characteristic for autoimmune thyroiditis, but for both processes (Hashimoto's thyroiditis and Riedel's thyroiditis), it is specific to the progressive introduction of glandular tissue and replacement with rigid, sometimes, scar tissue. According to molecular-biological research data, we can not exclude dysplastic and neoplastic transformation in progenitor cells during Hashimoto's thyroiditis versus Riedel's autoimmune Thyroiditis.

ACKNOWLEDGEMENTS

The research study was supported by A. Natishvili Institute of Morphology, Iv. Javakhishvili Tbilisi State University.

REFERENCES


Elizabeth N, Pearce MD, Alan P, Farwell MD, Lewis E, Braverman MD
Academia Journal of Scientific Research; Liana and Tamuna. 499


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