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THE IMPORTANCE OF ANTI PEROXIDASE ANTIBODIES IN PATIENTS WITH NODULAR THYROID GOITER

Abstract: *Introduction:* Thyroid nodular goiter is clinically recognizable restricted structure changes of the thyroid gland. Numerous studies show the relationship between thyroid autoimmunity and differentiated thyroid cancer in patients with nodular thyroid goiter. One of the important clinical marker in defining thyroid autoimmunity are antibodies to thyroid peroxidase. *Objective:* The aim of this study was to analyze the relationship between anti peroxidase antibodies and thyroid malignancy in patients with nodular thyroid goiter.

Material and Methods: We retrospectively reviewed the 248 reports of thyroid FNA cytology of samples obtained by puncture of patients with nodular thyroid goiter, at Department of thyroid gland, Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia in the period from October 2007. by January 2010. year. We analyzed the relationship between findings of cytopathological diagnostic categories and serum concentrations of anti peroxidase antibodies. The data were statistically processed using the computer program SPSS 12.0 software package.

Results: Of total 248 patients, 148 patients (59.7%) had anti-TPO antibody values in a reference limits (30 IU / ml), and 40.3% elevated anti-TPO antibodies (over 30 IU / ml). In the group of patients with elevated values of anti-TPO antibodies 7% (7/100) of patients had malignant cytologic findings, and in the group of patients with anti-TPO antibody values in the normal range only 1.4% (2/148) of patients had malignant cytologic findings.

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Conclusion: Defining the relationship between thyroid autoimmune disease and differentiated thyroid cancer, providing new insights in the field of immunotherapy of thyroid carcinoma. Enlightening the molecular mechanisms link autoimmune thyroid disease and thyroid cancer development in patients with thyroid nodule help find new therapeutic strategies against thyroid cancer.

Key words: thyroid nodule, anti peroxidase antibodies, thyroid autoimmunity, fine needle aspiration

Introduction:

Thyroid nodular goiter is clinically recognizable restricted structure changes of the thyroid gland. About 2-6% of the cases in this disease are discovered by palpation, 19-35% are discovered by sensitive procedures like ultrasound and 8-65% by autopsy. Prevalence is linearly increasing for years by exposure to radiation and iodine deficiency. It can occur endemically in areas with iodine deficiency. Women fall sick more often than man (1).

Clinical forms of the disease include non-toxic nodular goiter, multinodular toxic goiter and toxic thyroid adenoma (Plummer's disease).

Causes of the thyroid nodular disease can be benign (colloid nodules, Hashimoto's thyroiditis, simple or hemorrhagic cysts, follicular adenoma, subacute thyroiditis) and malignant (primary follicular cell origin-papillary, follicular and anaplastic thyroid carcinoma, origin of C-cell thyroid-modular thyroid carcinoma, lymphoma and secondary metastatic carcinomas).

Diagnosis of the disease is based on physical examination, laboratory testing, fine needle aspiration (FNA) and by visualization method (scintigraphy, ultrasound and ultrasound elastography, CT, MR and PET).

Fine needle aspiration (FNA) is crucial diagnostic procedure and first line of nodular thyroid goiter diagnostic tests. Qualification of diagnostic categories of thyroid FNA usually involves the following categories: 'malignant', 'benign', 'unspecified', 'unsuccessful'. The term refers to the indefinite lesions which based on cytological appearance couldn't be classified with certainty in one of the groups benign or malignant, and these include follicular, Hurthle cell and suspicious findings. Category was unsuccessfully related to those samples which didn't have enough material or the same material wasn't adequate for diagnosis.

Therapy is usually surgical or radioiodine ablation, while recently in indicated cases for that is applying recombinant therapy with human thyrotropin, percutaneous ethanol injection, laser thermal ablation and radiofrequency ablation.

Clinical significance of thyroid nodular diseases beside esthetic changes, such as neck thickening, local compressive syndromes and thyroid dysfunction is possibility

of developing malignancy in 5% cases. Annual incidence of thyroid carcinoma is 1-2 on 100.000 people, which makes 90% malignancy of the entire endocrine system, 1% of all malignancies in humans and 0,5% of mortality due to malignancy. (1,2).

Numerous studies show the relationship between thyroid autoimmunity and differentiated thyroid cancer in patients with nodular thyroid goiter.

One of the important clinical marker in defining thyroid autoimmunity are antibodies to thyroid peroxidase.

Objective

The aim of this study was to analyze the relationship between anti peroxidase antibodies and thyroid malignancy in patients with nodular thyroid goiter.

Material and methods

The study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the Clinical Center of Serbia in Belgrade. 248 reports of thyroid FNA cytology of samples obtained by puncture of patients with nodular thyroid goiter are retrospectively reviewed, at Department of thyroid gland, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia in the period from October, 2007 to January, 2010.

The patients were ambulatory examined, medical history is taken and laboratory tests were performed (biochemistry, blood test and hormonal status) ECG and ultrasound were performed and some patients had scintigraphy of the thyroid gland. After that (FNA) fine needle aspiration is performed, obtained preparations analysed in the Institute of Pathology in Clinical centre of Serbia in Belgrade.

Cytological examination of samples FNA are qualified by diagnostic category seed of thyroid FNA like: benign, malignant, unspecified and unsuccessful.

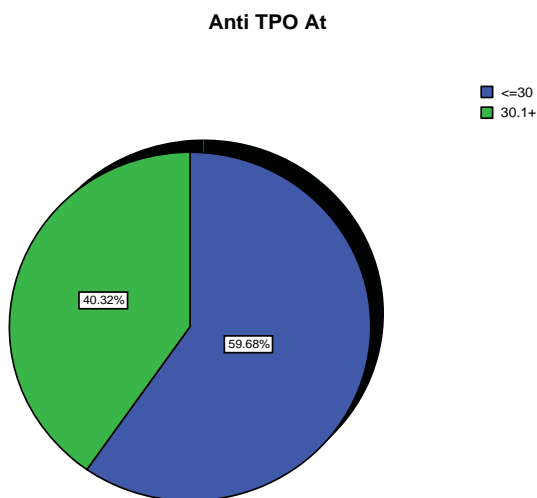
We analyzed the relationship between findings of cytopathological diagnostic categories and serum concentrations of anti peroxidase antibodies.

The data were statistically processed using the computer program SPSS 12.0 software package.

Results

Of total 248 patients, 148 patients (59.7%) had anti-TPO antibody values in a reference limits (30 IU / ml), and 40.3% elevated anti-TPO antibodies (over 30 IU / ml). The graphical results are shown in graph 1.

GRAPH 1: Distribution of antibodies TPO



The value of antibodies is examined in regard to diagnostic categories. Anti TPO antibodies values are divided in two groups and the first (to 30IU/ml) which includes normal values of antibodies and second (over 30IU/ml) which includes increased values of antibodies Table 1 shows the value of anti TPO antibodies by diagnostic categories.

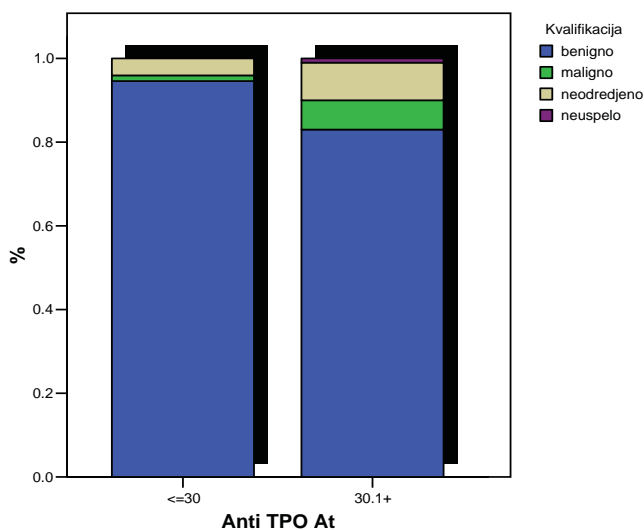
Table 1. Diagnostic categories depending on the value of anti TPO antibodies

		Diagnostic categories				Total	
		benign	malignant	unspecified	unsuccessful		
Anti TPO Ab	<=30	N	140	2	6	0	148
		%	94.6%	1.4%	4.1%	.0%	100.0%
	30.1+	N	83	7	9	1	100
		%	83.0%	7.0%	9.0%	1.0%	100.0%
Total		<u>N</u>	<u>223</u>	<u>9</u>	<u>15</u>	<u>1</u>	<u>248</u>
		<u>%</u>	<u>89.9%</u>	<u>3.6%</u>	<u>6.0%</u>	<u>.4%</u>	<u>100.0%</u>

The table shows that between patients with increased values of anti TPO antibodies even 7% of patients had malignant cytological findings, but in group of patients

with anti-TPO antibody values in the normal range only 1.4% (2/148) of patients had malignant cytologic findings. Results are graphically presented in the graph 2.

GRAPH 2. Anti TPO antibodies value depending on diagnostic categories (qualification)



Discussion

Hashimoto's thyroiditis and Graves' disease are two most common forms of thyroid autoimmunities, which characterize lymphocytic infiltration and auto-reactivity against thyroid autoantigens (3).

Thyroid peroxidase is the major enzyme involved in thyroid hormonal genetics, primarily identified like microsomal antigen. It's considered that these antibodies on this enzyme are the major cause of the thyroid gland inflammation. These antibodies are found in serum of patients with autoimmune diseases of thyroid gland. They are present in nearly all patients with Hashimoto's thyroiditis, in two-thirds of patients with postpartum thyroiditis and almost 75% of patients with Graves' hyperthyroidism. Anti peroxidase antibodies are produced by lymphocytes that in the state of inflammation infiltrate the gland, to a lesser extent lymphocytes that have origin of regional lymph glands and bone marrow. Antibodies damage the cells of the thyroid gland by induction antibody dependent cell mediated cytotoxicity.

Hashimoto's thyroiditis leads to development of hypothyroidism and to serum concentration and increase of thyrotropin hormone (TSH), while on the contrary of that Graves' disease, also with autoimmune nature, underlying the pathogenesis we have the growth of TSH concentration through TSH receptors stimulation. From referred

it could be assumed that the connection between humoral thyroid autoimmunity and thyroid malignancy is made through TSH receptors.

The results of our study show that from 248 patients, 148 of patients (59,7%) had anti TPO antibody values in the normal limits (to 30IU/ml), but 40,3% had the increased values of anti TPO antibodies (over 30IU/ml). In the group of patients with increased values of anti TPO antibodies even 7% (7/100) of patients is with malignant cytological findings, and in group of patients with anti TPO antibody values in normal limits is only 1.4% (2/148) with malignant cytological findings.

Based on the results it may be noted significantly higher proportion of patients with malignant cytological findings and with increased values of anti peroxidase antibodies. Numerous studies that have been done examined the connection between autoimmune thyroid disease and differentiated thyroid carcinoma.

Even if there isn't an agreement of all, target analysis of 10 studies by Singh and collaborators has shown that with patients who have Hashimoto's thyroiditis have even 2.77 times higher risk for appearance of thyroid malignancy compared with the control group. Boelaert and collaborators in study done in 2006 have shown significantly higher frequency of cancer in patients with the present anti peroxidase antibodies in comparison with patients where were present antibodies.

Contrary to already specified, the study of Fiore and collaborators shows that between the patients with anti peroxidase positive and negative antibodies there is no difference in frequency of thyroid malignancy. The study Rebuffat with collaborators has shown that anti TPO antibodies achieve cell-mediated cytotoxicity and antiproliferative activity in papillary thyroid carcinoma cells (4).

Based on numerous studies it's accepted that focal chronic lymphocytic thyroiditis (whether it's nonspecific or Hashimoto's) leads to the development of malignancy, while the connection between diffuse chronic thyroiditis and thyroid malignancy still remains unclarified.

Conclusion

Defining the relationship between thyroid autoimmune disease and differentiated thyroid cancer, providing new insights in the field of immunotherapy of thyroid carcinoma. Enlightening the molecular mechanisms link autoimmune thyroid disease and thyroid cancer development in patients with thyroid nodule help find new therapeutic strategies against thyroid cancer.

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