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Hashimoto's thyroiditis is not a risk factor for thyroid cancer

Mohsen Eshraghi* and Seyed Mojtaba Mousavi***ABSTRACT****BACKGROUND**

Thyroid carcinoma is the most common endocrine malignancy. Chronic inflammation can be involved in tumorigenesis. It is estimated that more than 20% of all tumors are caused by persistent inflammatory conditions. The objective of the present study was to compare the inflammatory factor level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and thyroiditis between benign and malignant thyroid nodules.

METHODS

A cross-sectional study was conducted involving 94 patients (47 patients with benign tumors as controls and 47 patients with malignant tumors as cases). ESR and CRP were measured and analyzed. Mean ESR and CRP in both groups was compared using independent t-test. The chi-square test was used to assess the risk of cancer in patients with Hashimoto's thyroiditis and with significance level at $p < 0.05$.

RESULTS

The mean age of the patients in the benign group was 42.28 ± 13.43 years and in the malignant group 42.20 ± 16.32 (20-85) years, which was not significantly different ($p=0.350$). Independent t-test results were not significantly different between mean ESR and CRP in both groups ($p=0.800$ and $p=0.993$ respectively). Hashimoto's thyroiditis was not a risk factor for thyroid cancer (OR=1.58; 95% CI:0.63-4.01).

CONCLUSION

This study demonstrated that Hashimoto's thyroiditis was not a risk factor for thyroid cancer. Factors such as ESR and CRP are acute phase reactants and their levels increase in cases of acute inflammation, but may not increase significantly in chronic inflammatory conditions and malignancies.

Keywords: Thyroid nodules, CRP, ESR, thyroiditis subjects

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy, and the incidence has been increasing worldwide during the last decades.^(1,2) Thyroid cancer occurred in 8.7 per 100 000 individuals in 2002 according to the Surveillance, Epidemiology, and End Results (SEER) database.⁽³⁾

Papillary thyroid carcinoma (PTC) is the most frequent (64.21%) of all TCs, and follicular thyroid carcinoma (FTC) 6.37% is the second thyroid malignancy according to frequency, followed by medullary thyroid carcinoma (MTC) (5.88%) and anaplastic thyroid carcinoma (ATC) (5.39%).⁽⁴⁾

Most thyroid nodules are benign with “atypia of undetermined significance” (AUS)/ “follicular lesion of unknown significance” (FLUS) cytology and benign follicular neoplasm.⁽⁵⁾

Thyroid gland lymphoma often occurs in the case of Hashimoto’s thyroiditis. A rapidly growing thyroid mass should lead the physician to suspect this diagnosis.⁽⁶⁾ The diffuse lymphoma with large cells is the most common type of thyroid lymphoma. On biopsy, there are laminae of lymphoid cells that are difficult to differentiate from small cell lung cancer or anatomical therapeutic chemical (ATC) code system. These tumors often have a high sensitivity to external radiation.⁽⁷⁾ Surgical resection should be avoided as a primary treatment, as this may lead to the spread of the disease. Otherwise, it remains limited to the thyroid gland. If staging indicates the presence of the disease outside the thyroid gland, treatment should be continued based on the treatment of other forms of lymphoma.⁽⁸⁾

In a study by Heikkila et al.⁽⁹⁾ clinical and molecular aspects and the expression of inflammatory genes were investigated in a large group of patients with papillary thyroid cancer (PTC) with and without related thyroiditis. In general, patients with cancer have been shown to have higher C-reactive protein (CRP) concentrations than healthy controls and

participants with some benign diseases.⁽⁹⁾ In conclusion, most of the studies attempting to evaluate the use of circulating CRP in the diagnosis of various cancers did not present relevant statistical analyses and most of the vast literature published on the association of circulating CRP with cancer has been based on studies of prevalent cancer cases, which cannot provide evidence for causality. The small number of prospective studies identified in this review did not provide strong evidence for a causal role of CRP in malignancy, although there was some evidence that CRP could be related to colorectal cancer in particular. Further prevalent studies in this area will not add to what is already known; more large prospective studies and studies examining the association of CRP functional genetic variants with cancer outcomes would be useful to determine the role of CRP in the etiology of cancer.

In a study by Allin et al.,⁽¹⁰⁾ the purpose of this study was to investigate the relationship between CRP and risk of cancer, and whether increasing CRP can be a cause of cancer. In addition, this study provides information on the response of the phase of chronic inflammation, molecular biology, performance and measurement of CRP, cancer prognosis and cancer biomarkers.

In a study in the general population of Copenhagen⁽¹¹⁾ on around 63,500 people, about 97% of participants had a CRP level below 10mg/L. The mean plasma CRP levels (IQR, 1.14-2.51) were 1.53 mg/L, and 34% had CRP >2mg/L. Epidemiological studies suggest that in patients with solid tumors, increased levels of CRP are associated with poor prognosis, while in seemingly healthy people, elevated CRP levels are associated with an increased risk of lung cancer and possibly colorectal cancer, but not prostate cancer. The lack of causality between increased levels of CRP and increased risk of cancer does not invalidate the clinical application of a mild increase in CRP levels to predict the risk of cancer types and treat cancer patients.⁽¹²⁾

In a study by Hou et al.,⁽¹³⁾ 512 patients, consisting of 341 patients with PTC and 171

patients with nodular goiter, were included in the study. In patients with PTC, the mean ESR level was 11.35 ± 14.24 mm/h which was lower than in those with nodular goiter (16.90 ± 12.00 mm/h, $p=0.006$). The mean CRP level was 1.81 ± 3.51 mg/L in the PTC group, which was lower than that in the nodular goiter group (2.09 ± 3.34 mg/L, $p=0.008$).

Lee et al.⁽¹⁴⁾ analyzed data from 38 published studies that assessed the association between thyroid cancer and Hashimoto's thyroiditis (HT). Hashimoto thyroiditis is more common in papillary cancers (40%) than in benign thyroid nodules (21%), in female patients (23%) than in males (11%), and in papillary thyroid (17%) compared to other types of thyroid cancer (8%). This meta-analysis revealed that PTC who had HT had a lower chance of recurrence than patients with papillary congestion without HT.

A study by Replinger et al.⁽¹⁵⁾ investigating the association between Hashimoto's and PTC's thyroiditis in women showed that HT was associated with an increased risk of PTC.

A study by Jankovic et al.⁽¹⁶⁾ using data from population-based fine needle aspiration (FNA) studies did not find a statistically significant correlation between HT and PTC. Another study did not observe such an association between HT and thyroid cancer.⁽¹⁷⁾ Therefore, the recent notion that neoplastic thyroid transformation is capable of creating a small neurogenic proinflammatory environment has tended to result in further studies on thyroid autoimmune PTC. Therefore the goal of the present study was to compare the inflammatory factor level of ESR, CRP and thyroiditis between benign and malignant thyroid nodules.

METHODS

Research design

This observational study, which was a cross-sectional analytical study of diagnostic type, involved patients with cold thyroid nodules referring to Shahid Beheshti Hospital of Qom in 2014.

Research subjects

Patients who were referred to the thyroid gland department were selected using a purpose-based sampling method. Erythrocyte sedimentation rate and CRP was measured before surgery in patients who were candidates for thyroid surgery. Thyroid nodules were divided into two groups: benign (control) and malignant nodules (the case group) according to the pathology report. The required number of samples in each group was 47, and the standard deviation in each group was considered to be 5.7 according to the same article.⁽¹⁸⁾ The two groups were matched in terms of age and sex. The criteria for entry in this study were patients who had undergone surgery due to thyroid nodules, and whose CRP and ESR were measured before surgery.

Biochemical assays

ESR measurement was according to standard laboratory methods on the sedimentation rate of red blood cells. A fixed amount of blood is drawn into a vertical tube with sodium citrate as anticoagulant. The Wintrobe method is performed similarly to the Westergren method except that the Wintrobe tube is smaller in diameter than the Westergren tube and only 100 mm long. The shorter Wintrobe column makes this method less sensitive than the Westergren method because the maximal possible abnormal value is lower. EDTA anticoagulated blood without extra diluent is drawn into the tube and the blood sample is thoroughly immediately prior to testing. The blood is then left to settle for 1 hour, after which the distance between the top of the blood column and the top layer of the red blood cells (RBCs) below is measured. The ESR is thus expressed in millimeters/hour.

CRP was measured using the quantifies C-reactive protein (CRP) by latex-enhanced nephelometry and reported in mg/L. The test requires no instrumentation and is available in two variants, one for serum, the other for \bar{y} blood. In each sample application position, the diluted

Table 1. Demographic and laboratory characteristics according to pathological results of patients enrolled in the study

Variable	Malignant group (n=47)	Benign group (n=47)	p value
Age (years)	45.20 ± 16.32	42.28 ± 13.43	0.350
Sex, female (%)	39 (83.0%)	39 (83.0%)	0.560
Tumor size (cm)	17.64 ± 9.31	40.16 ± 28.81	0.009
ESR (mm/h)	13.54 ± 8.09	13.03 ± 7.80	0.800
CRP (mg/L)	5.88 ± 4.92	6.02 ± 4.91	0.993

ESR : erythrocyte sedimentation rate; CRP : C-reactive protein

sample is applied on top of a membrane γ coated with monoclonal antibodies directed against CRP. The bound CRP is then detected and γ measured using a gold-conjugated monoclonal CRP-antibody. The amount of this secondary γ antibody bound to the membrane is directly proportional to the CRP concentration in the sample. CRP was measured by immunoturbidimetry or nephelometry with a CRP of ≥ 0.5 mg/dL being considered abnormal while ESR was measured using the Westergren method with >25 mm/h being considered as abnormal. More relevant clinical elevations were also examined, being defined as any measure which was twice the elevated cutpoint. Each laboratory reading was compared on an individual basis as a mean for each patient and on a collective group basis.

Statistical analysis

ESR and CRP were measured before surgery and were compared by independent t-test in two groups. Factors such as age, sex, and history of thyroiditis were also compared in two groups. An independent-t test and chi-square test were used to analyze the data. A p value <0.05 was considered statistically significant.

Ethical clearance

This investigation was approved by the Research Ethics Committee Shahid Beheshti Hospital of Qom (IR.MUQ.REC.1395.121) and informed consent was obtained from the patients. The patients were assured that their information were to be kept confidential and would be used only for research purposes.

RESULTS

The number of patients in each group and the total by sex was 94 patients (78 women and 16 men) divided into two groups of 47 each, comprising 39 females and 8 males. The mean age of the patients in the benign group was 42.28 ± 13.43 (22-70) years and in the malignant group 42.20 ± 16.32 (20-85) years, which was not significantly different ($p=0.350$). Mean ESR in the benign and malignant groups was compared using the independent t-test. There was no significant difference in mean ESR levels between the two groups ($p=0.800$). Mean CRP in the benign and malignant groups also showed no significant difference ($p=0.993$) (Table 1).

The rate of thyroiditis in both benign and malignant groups was evaluated and compared. In the benign group according to the pathological report, 15 patients (31.9%) had a history of Hashimoto's thyroiditis, while in the malignant group, a history of Hashimoto's thyroiditis was reported in 20 patients (42.6%). Hashimoto's thyroiditis (HT) increased the risk of cancer, but the increase was statistically not significant (O.R.=1.5;95% Confidence Interval 0.63-4.01).

DISCUSSION

The mean ESR level was similar between the benign and malignant groups. Contrary results were found in a study by Hou et al.,⁽¹³⁾ in that in patients with PTC the mean ESR level was significantly lower than in those with nodular

nodular goiter. The mean CRP level was also similar between the benign and malignant groups. In the study of Hou et al.,⁽¹³⁾ the mean CRP level in the PTC group was significantly lower than that in patients with nodular goiter.

The reason for the difference in the ESR and CRP results between the present study and that by Hou et al.⁽¹³⁾ may be due to differences in the samples and the genetic backgrounds of the two populations. In the Hou study there was no homogeneity in the numbers of patients in the two groups, which can be one of the reasons for the difference between the results of the two studies. In the present study, homogeneity between the two groups was attained. Hashimoto's thyroiditis was not a risk factor for thyroid cancer in our study. This result was in line with the study of Heikkila et al.⁽⁹⁾ and Anil et al.⁽¹⁷⁾

However, the study of Krátký al.⁽¹⁹⁾ showed that HT was found to be higher in papillary cancer compared to benign thyroid nodule. However, a study conducted by Jankovic et al.⁽¹⁶⁾ in population-based FNA studies did not find a statistically significant correlation between HT and PTC. At the present time, there is no valid established criterion to identify those patients with HT at a higher risk of developing PTC. Careful observation and follow-up of HT patients is recommended, especially those with nodular variants. This study had a few limitations. First, the factors such as income level, alcohol consumption history, metastasis, diagnostic and treatment method are some factors affecting on the survival level, the effect of which may be a limitation in the present study. Second, the tumor type in all patients was PTC in the malignant group, while the relation between ESR/CPR level and other inflammatory factors such as IL-1.6 and other thyroid cancers such as follicular, nodular, anaplastic, and also thyroid lymphoma can be studied.

It is also suggested that further studies are needed to investigate the relationship between the level of antithyroid antibodies such as thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) with the type of nodule (benign with

malignant) and the size of the nodule. And in the case of malignant nodules, the association of these antibodies with nodule invasion into thyroid capsules, blood vessels, lymph nodes, and prognosis and patient survival should be considered.

CONCLUSION

According to this study, it can be concluded that factors such as ESR and CRP that are considered acute phase reactants and the levels of which increase in acute inflammatory conditions may not increase significantly in chronic inflammatory and malignant conditions. Hashimoto's thyroiditis was not a risk factor of thyroid cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONTRIBUTORS

ME wrote the paper and designed the study. SMM contributed to data collection and analysis. All authors have read and approved the final manuscript. 

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