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CLINICAL STUDY

Influence of autoimmune thyroiditis on the prognosis of papillary thyroid carcinoma

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ABSTRACT

OBJECTIVES: The association of autoimmune thyroiditis (AIT) with papillary thyroid carcinoma (PTC) has been studied for over 60 years, yet their causal relationship has not been elucidated. Most published papers report a better prognosis of the patients with tumour in the field of thyroiditis. In our work we aimed to find out the differences in the clinical behaviour of PTC depending on the presence of autoimmune inflammation.

METHODS: We retrospectively analysed a group of 1,201 patients with PTC dispensed in St. Elisabeth Cancer Institute and Faculty of Medicine from 2000 to 2015. We divided patients with AIT according to the time of diagnosis of inflammation into the AIT1 subgroup, which included patients monitored for AIT before tumour detection. In them, we assumed that the factor of long-term endocrinological monitoring could speed up the diagnosis of the tumour and thus improve the prognosis. The AIT2 subgroup consisted of patients with both tumour and inflammation diagnosed simultaneously, thus eliminating the factor of prior monitoring.

RESULTS: PTC in the AIT1 subgroup had better prognostic parameters (TNM stage, persistence, disease remission). Patients in the AIT2 group had all monitored parameters comparable with patients with tumours without autoimmune inflammation.

CONCLUSION: AIT alone does not have a protective effect on the course of PTC, the cause of a better prognosis in the AIT1 subgroup is a different pathomechanism of carcinogenesis, as well as previous endocrinological monitoring and earlier detection of malignancy *(Tab. 4, Fig. 2, Ref. 27)*. Text in PDF *www.elis.sk*

KEY WORDS: papillary thyroid cancer, autoimmune thyroiditis, relationship, carcinogenesis prognosis.

Introduction

The association of AIT with thyroid cancer was first described by Dailey in 1955 (1). Since then, several papers have been published on the relationship between the AIT and PTC, but the question of whether this relationship is causal or accidental remains unanswered. In particular, AIT is discussed as a risk factor in the development of PTC and, conversely, as a possible protective effect of AIT in the process of carcinogenesis (2, 3, 4).

The relationship between AIT and PTC has been examined at different levels. There is evidence of an epidemiological link: the prevalence of AIT is significantly higher in patients with PTC as compared to the rest of the population, while both diseases are equally more common in women. At the pathophysiological level, there was found an increase in the expression of cyclooxygenase 2 (COX-2) in thyrocytes of patients with AIT and differentiated thyroid carcinoma (papillary and follicular carcinoma), but not in patients with normal thyroid, multinodular goitre and anaplastic (undifferentiated) thyroid carcinoma (5). At the molecular pathological level, AIT may exhibit cytological changes and nuclear modifications like those present in PTC(6, 7). Biomolecular markers that could be involved in the neoplastic transformation of AIT to PTC include RET/PTC rearrangements, p63 protein, BRAF mutations, and PI3K/Akt (8, 9). The malignant transformation of the thyroid gland can be caused not only by cellular mediators produced by immune cells in the state of chronic inflammation, but also by increased levels of TSH in hypothyroidism, which stimulates the proliferation of follicular epithelium (10). The association between AIT and PTC is also suggested by several large retrospective and prospective cytology studies. Similar results were obtained from surgical and pathological studies where the association of AIT and PTC was based on the evidence of lymphocyte infiltrate in combination with thyroid carcinoma in histological examination (11, 12).

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The results of many studies dealing with pathogenetic immunological relationships of AIT and PTC can be divided into three categories of hypotheses as follows:

1) AIT arises in response to pre-existing PTC

Thyroid cancer can elicit an autoimmune response by inducing a pro-inflammatory transcription program of the RET/PTC oncogene. Oncogenes responsible for neoplastic transformation of cells create a pro-tumour inflammatory environment. Pro-inflammatory molecules such as cytokines and chemokines produced by the inflammatory infiltrate of the tumour microenvironment contribute to the regulation of cellular processes of tumour formation and progression, in particular cell proliferation, apoptosis, angiogenesis, and metastasis.

The lymphocytic inflammatory infiltrate around the tumour is thought to form cytotoxic T cells that can kill tumour cells. This explains the better prognosis of patients with cancer in the field of AIT (7, 13). According to several studies, coincidental AIT is associated with a lower stage of the disease and PTC in the field of AIT behaves less aggressively (14, 15). Chronic inflammation is thought to act as a protective factor in tumour progression.

2) PTC arises based on or is at least supported by the pre-existing chronic inflammatory process

Chronic inflammation can cause carcinogenesis by promoting genomic instability. Molecular studies have shown that thyrocytes can induce COX-2 and produce interleukin-6 under the influence of interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) (26). Increased COX-2 expression is known to be associated with carcinogenesis of various tumours by inhibiting apoptosis and promoting angiogenesis. COX-2 expression has been demonstrated in both thyroid carcinoma and AIT thyrocytes, but not in normal thyroid tissue (16). Chronic inflammation may also potentiate the genetic rearrangement of the RET/PTC oncogene with subsequent activation of the MAPK signalling cascade, which is a driving force in the development of PTC in the AIT field (13). RET/PT remodelling has been demonstrated in benign thyroid cells in both AIT and PTC patients (17). It has also been shown in familial PTCs associated with AIT (18).

3) Common pathogenetic mechanisms are responsible for both diseases (19)

Materials and methods

Patients characteristics

We included all patients with PTC treated at St. Elisabeth's Cancer Institute from 2000 to 2015, for whom we had all monitored parameters. We did not include patients who left our dispensary care during their follow-up. We included only patients monitored until 2015, because up to then all patients with PTC from western Slovakia had been monitored at our workplace. Since 2015 many low-risk patients have been monitored by district endocrinologists. The results would therefore not be objective.

A total of 1,201 patients with PTC were enrolled (984 women, 217 men). The mean age of patients with PTC without AIT was 48 years, while in those with PTC and AIT, it was 47.7 years. The differences were not statistically significant.

The diagnosis of chronic autoimmune thyroiditis was based on histological evidence of diffuse thyroid lymphocytic infiltrate and/or positivity of aTPO and/or aTg. We did not evaluate the focal lymphocyte infiltrate around the tumour as AIT. The level of autoantibodies at least twice the upper limit of the norm was considered positive. The levels of aTPO and aTg were determined by the immunochemiluminescence method with commercial kits from Abbott, on an Architect i2000SR analyser.

Methods

We retrospectively analysed the patient's age at the time of tumour diagnosis, sex, histological type and variant of the tumour, number of primary tumour foci, TNM stage, levels of thyroid autoantibodies aTPO and aTg, presence of diffuse lymphocyte infiltrate in histological findings, time relationship of diagnosis of AIT and cancer, number of operations, cumulative dose of radioiodine, patient prognosis – presence of remission and persistence/recurrence of the disease after 5 years of treatment.

Statistical methods

Clinical characteristics were analysed by methods of descriptive and inferential statistics. Numerical characteristics (such as age, dose) were described by arithmetic mean. Non-numeric, i.e., categorical characteristics were given as absolute and relative abundances (percentages of the defined whole). Subsequently, the mutual bivariate relationships between the predictor of AIT interest and other clinically relevant characteristics were studied. Intergroup differences in numerical characteristics were tested by unpaired t-test. In the case of deviation from the normal distribution, the consistency of the conclusion on statistical significance by the nonparametric Mann-Whitney test was verified. The chi-square (χ^2) test was used to test for intergroup differences in categorical characteristics. If the conditions for the use of these tests have not been met due to low numbers, the exact Fisher test was applied. The magnitude of the effect, i.e., the ratio of the occurrence of the characteristic in the compared groups, is presented as the odds ratio (OR, odds ratio).

The analyses were performed using a Microsoft Excel spreadsheet program within Office 365 (Microsoft Corporation) and StatsDirect 3.3.4 statistical software (StatsDirect Ltd., Cheshire, UK).

Results

A total of 1,201 patients were included in the cohort. Of the total group, AIT was present in 498 patients, which is 41.5 %. Patients with AIT were further divided into two subgroups according to the time course of diagnosis of AIT and PTC, particularly 330 patients had AIT diagnosed before tumour (AIT1), 168 patients were diagnosed with AIT and tumour concurrently (AIT2). The basic numbers of individual categories are made clear by displaying them graphically (Fig. 1).

Of all 498 patients with autoimmune thyroiditis-associated PTC, 330 patients (27.5 %) had been diagnosed with AIT and endo-

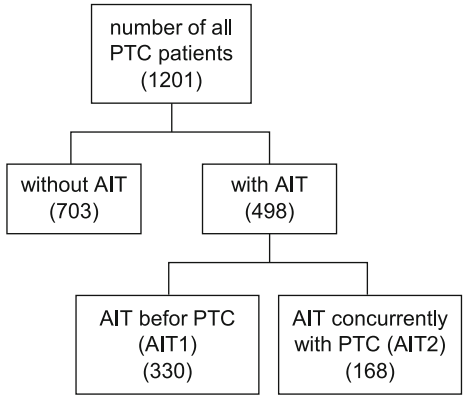

Fig. 1. Basic characteristics of the cohort.

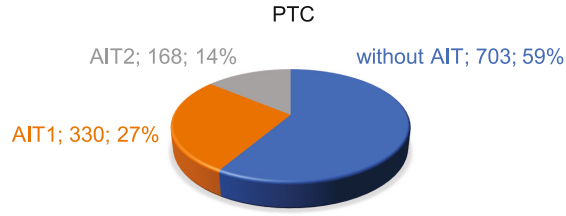

Fig. 2. Occurrence of AIT in patients with PTC.

crinologically monitored before the tumour was recognised (AIT1 group), while 168 (14 %) patients with PTC had their AIT and tumor diagnoses established simultaneously (AIT2 group) (Fig. 2).

Comparison of stand-alone PTC with AIT-associated PTC

As compared to stand-alone PTCs, AIT-associated PTCs were more frequently multifocal (31 % vs 26 %) and more often microcarcinomas (27 % vs 20 %; $p < 0.05$) with less frequently repeated surgery (11 % vs 17 %) and less common persistence or recurrence of the disease after five years of tumour diagnosis was observed (5 % vs 12 %). All these differences were statistically significant. We found no statistically significant differences in the presence of aggressive histology (8 % vs 6 %), low-risk tumour (T1-2N0M0) (60 % vs 56 %), high-risk (N1b (21 % vs 24 %), M1 (2 % vs 4 %)) and larger tumours (T3 (13 % vs 13 %) and T4 (7 % vs 10 %)) and in remission after 5 years (71 % vs 67 %) (Tab. 1).

Comparison of stand-alone PTC and AIT-associated PTC in patients endocrinologically monitored before tumour detection (subgroup AIT1)

By comparing stand-alone PTC with AIT-associated PTC in AIT1 subgroup, we found no statistically significant differences

Tab. 1. Comparison of PTC without AIT with PTC in the field of AIT.

	Number of patients without AIT	% of patients without AIT	Number of patients with AIT	% of patients with AIT	Statistical significance $p < 0.05$	OR
Aggressive histology	46	6	39	8	NS	0.82
Multifocality	183	26	156	31	< 0.05	0.77
T1-2N0M0	392	56	300	60	NS	0.83
Microcarcinoma	143	20	134	27	< 0.05	0.69
N1b	168	24	105	21	NS	1.18
M1	26	4	11	2	NS	1.7
T3	93	13	63	13	NS	1.05
T4	72	10	36	7	NS	1.46
Repeated surgery	116	17	58	11	< 0.05	1.5
Persistence/recurrence	82	12	25	5	< 0.05	2.50
Remission	468	67	352	71	NS	0.83

Tab. 2. Comparison of PTC without AIT with PTC in the field of AIT in monitored patients before tumor detection (subgroup AIT1).

	Number of patients without AIT	% of patients without AIT	Number of patients without AIT1	% of patients without AIT1	Statistical significance $p<0.05$	OR
Aggressive histology	46	6	24	7	NS	0.89
Multifocality	183	26	111	34	< 0.05	0.69
T1-2N0M0	392	56	219	66	< 0.05	0.64
Microcarcinoma	143	20	99	30	< 0.05	0.60
N1b	168	24	52	16	< 0.05	1.68
M1	26	4	1	0.3	< 0.05	8.80
T3	93	13	31	9	NS	1.47
T4	72	10	21	6	< 0.05	1.68
Repeated surgery	116	17	21	6	< 0.05	2.91
Persistence/recurrence	82	12	12	3.6	< 0.05	3.12
Remission	468	67	248	75	= 0.05	0.66

Tab. 3. Comparison of stand-alone PTC with AIT-associated PTC in unmonitored patients (subgroup AIT2).

	Number of patients without AIT	% of patients without AIT	Number of patients without AIT2	% of patients without AIT2	Statistical significance p<0.05	OR
Aggressive histology	46	6	15	9	NS	0.71
Multifocality	183	26	45	27	NS	0.96
T1-2N0M0	392	56	81	48	NS	1.35
Microcarcinoma	143	20	35	21	NS	0.97
N1b	168	24	53	32	< 0.05	0.68
M1	26	4	10	6	NS	0.61
T3	93	13	32	19	NS	0.65
T4	72	10	15	9	NS	1.22
Repeated surgery	116	17	37	22	NS	0.7
Persistence/recurrence	82	12	13	8	NS	1.57
Remission	468	67	104	62	NS	1.23

Tab. 4. Comparison of median cumulative radioiodine dose of individual PTC groups with AIT (AIT in total, AIT1, AIT2) with PTC without AIT.

	Median cumulative radioiodine dose in PTC without AIT (mCi 131I)	Median cumulative dose in each PTC group with AIT (mCi 131 I)	Statistical significance p<0.05
AIT patients in total	207	236	NS
subgroup AIT1	207	191	NS
subgroup AIT2	207	262	NS

in the proportion of aggressive histology (6 % vs 7 %). PTC in the AIT1 subgroup compared to stand-alone PTC had more frequent multifocal tumours (34 % vs 26 %), low-risk tumours (T1-2N0) (66 % vs 56 %) and microcarcinomas (30 % vs 20 %) with less frequent nodular metastases in the lateral cervical compartment (16 % vs 24 %), distant metastases (0.3 % vs 4 %) and larger primary tumours (T3: 9 % vs 13 %, 6 % vs 10 %).

Patients with PTC in the AIT1 subgroup had less frequently repeated surgery (6 % vs 17 %), more frequently achieved disease remission after 5 years (75 % vs 67 %). %) and more rarely the disease persisted/relapsed (8 % vs 12 %). All these differences were statistically significant (Tab. 2).

Comparison of stand-alone PTC with AIT-associated PTC in the unmonitored patients (subgroup AIT2)

Patients with PTC in the AIT2 subgroup had only statistically significant increase in the N1b stage (32 % vs 24 %) compared to patients with PTC without AIT. Differences in other endpoints reflecting tumour aggressiveness did not reach statistical significance (Tab. 3).

Median cumulative radioiodine dose in patients with PTC

In individual groups of AIT-associated PTC, we found no statistically significant differences in the median cumulative dose of radioiodine as compared to PTC without AIT (Tab. 4).

Summary of results and their interpretation

1. Patients with PTC in subgroup AIT1 had better prognostic parameters as compared to PTC without AIT. These favourable indicators were logically due to the long-term follow-up of patients and detection of tumours at an earlier stage. Paradoxically, however, despite the multi-year follow-up, PTC in the AIT1 subgroup was not detected at a significantly younger age. From this we could conclude that PTC induced by autoimmune thyroiditis is a less aggressive tumour *per se*, progresses more slowly and the capture in the earlier TNM stage is caused not only by the fact of patients being previously monitored but also by the milder biological nature of such induced tumours.
2. The PTC in AIT2 subgroup had prognostic parameters comparable to PTC without AIT. In addition, we found a statistically significantly more frequent occurrence of nodal metastases in the lateral cervical compartment. Thus, the prognosis of these tumours in the field of AIT was not better as compared to tumours without AIT. In the AIT2 group, we assume the development of AIT only after the development of cancer. In this case, the secondary onset of AIT is not a protective factor against PTC.
3. AIT had no effect on the occurrence of aggressive histological variants of PTC. The better prognosis of PTC in the AIT1 group is not due to a less aggressive histological variant of the tumour.

Discussion

The literature reports a better prognosis of patients with PTC in the field of AIT. It is explained by the "protective effect" of AIT in the process of carcinogenesis, but no precise mechanism has been elucidated. It is thought that thyroid autoantibodies present in patients with AIT may possibly also attack malignant thyrocytes, and thus contribute to a better prognosis. There are data on smaller tumour size, lower incidence of metastases, lower risk of disease persistence in PTC in the field of AIT (20–26).

In our cohort, low-risk tumours and microcarcinomas were more frequent only in the AIT1 subgroup. Patients in the AIT1

subgroup had tumours diagnosed at an earlier stage but were not younger than patients with tumours without AIT. Thus, the cause of the earlier stage of the tumour lied not only in the acceleration of the diagnosis of malignancy due to the endocrinological follow-up before the detection of the tumour. We hypothesize that the autoimmune inflammation, which initiated the carcinogenesis, was primarily present in these patients. These tumours grow slowly and have a better prognosis. In the subgroup AIT2, which had worse prognostic indicators, we assume a secondary induction of autoimmune inflammation by tumours. These tumours behave more aggressively.

Many studies report a higher incidence of multifocality in PTC associated with AIT as compared to tumours without AIT (31–46 % vs 23–27 %) (12, 27). A meta-analysis of twelve studies involving 1,378 patients with multifocal PTC and 2,549 patients with unifocal PTC had AIT present in 359 (26 %) multifocal tumours and 541 (21 %) unifocal tumours (25). In our cohort, higher multifocality was associated only with PTC subgroup AIT1 (PTC with AIT 34 % vs PTC without AIT 26 %). We explain this by our theory that in this group of patients, long-lasting autoimmune inflammation induced tumour formation. In the AIT2 subgroup, we hypothesize that the tumour triggered AIT, which is associated with a lower incidence of multifocality in these patients.

The data on association of AIT with the histological variant of PTC are scarce (27). In our cohort, we found no statistically significant differences in the presence of aggressive histological variants of PTC depending on the presence of AIT. In PTC, patients with AIT had even a higher incidence of aggressive variants than patients without AIT, but this difference did not reach statistical significance. Based on these findings, we can conclude that the apparent protective effect of AIT is not related to the histological variant of the tumour.

More aggressive histological variants of PTC in AIT-associated tumours have been identified in the Egyptian population (27). Tall cell variant PTC, Hurthle carcinoma, FTC and dedifferentiated forms of tumours were more common. In patients with AIT-associated tumours, they also observed the same degree of metastatic lymph node involvement and extrathyroidal tumour spread as compared to patients without AIT. The authors hypothesize that endemic iodine deficiency in Egypt in the Nile basin may be at least partly responsible for the greater aggressiveness of the tumour.

Conclusions

Based on our finding that the significant differences in the behaviour of AIT-associated PTC depend on the time of diagnosis of AIT, we assume that different pathomechanisms of carcinogenesis are responsible for the development of PTC in AIT patients. Further studies are needed to confirm this hypothesis. Better understanding of pathomechanism of PTC carcinogenesis can provide more targeted therapeutic approach to each individual patient.

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