Relationship between autoimmune thyroiditis and papillary thyroid cancer

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Topic: Thyroid Cancer 1; GP225

Backgroud:

Coexistence of autoimmune thyroiditis (AIT) and papillary thyroid cancer (PTC) has been well documented, but causality is still a matter of debate. AIT and PTC share some common features: 1/ epidemiological: increasing incidence, 2/ morphological: PTC-like nuclear alterations in thyrocytes from AIT, 3/ immunohistochemical pattern: PTC-associated proteins: galectin 3, cytokeratin 19, fibronectin 1, etc, 4/ molecular profile: RET/PTC rearrangement, BRAF mutation (V600E), etc...
Pathogenetic links between PTC and AIT try to explain two theories: 1/ PTC is induced or facilitated by AIT. Chronic inflammation can stimulate carcinogenesis by inducing genomic instability. 2/ PTC is able to induce immune response. AIT is a response to PTC. It is believed that PTC associated to AIT has a better prognosis and survival.
Since seventies we have been facing an „epidemy" of AIT. Even in the population of adolescent girls 5% of them are affected. It is generally believed that the development of autoimmune thyroid disease depends on complex interactions between genetic, environmental and endogenous factors. Iodine excess belongs to the most important environmental risk factors.
Slovakia is a country with sufficient iodine intake due to a long-term iodine prophylaxis.
The number of differentiated thyroid cancer (DTC) patients admitted for radioiodine treatment to our institution doubled during last decade.

Aims:

to find out
a/ the incidence of AIT in DTC/PTC patients,
b/ the course of PTC associated to AIT,
c/ the relationship between these diseases.

Methods:

Histological and laboratory results of 1251 DTC patients from the period 2005-2012 were reviewed. Diagnosis of AIT was based on histological finding and/or high antiTPO level (> 3-times above upper reference range limit).

Results:

The incidence of AIT in DTC patients was 41%, 3-4-times higher compared to the general population
DTC associated to AIT was diagnosed in younger age of patients (mean 6 years) and with less advanced clinical picture compared to patients without AIT. Among DTC patients the incidence of PTC was even higher **(95%)** and the predominance of women was even more marked **(92%)** compared to patients without AIT.
PTC patients with coexisting AIT compared to that without AIT had better prognostic indicators (staging according to TNM classification), e.g. significantly higher incidence of small cancers and microcarcinomas (T1) and lower incidence of distant metastases. Lower cumulative dose of radioidine was used in them to achieve remission. Persistence rate after 5 years of treatment was lower compared to PTC patients without AIT (Tab 1 and Tab 2). These data at first sight support the hypothesis, that AIT has a protective role against progression of PTC. A more comprehensive analysis of data brought an opposed opinion.
These illusory favourable findings were indeed caused by the fact, that 65% of AIT patients were already followed-up for this disease for several years and PTC developed and was detected during this period (Tab 3). When we compared prognostic indicators of PTC patients without AIT with those of PTC patients where AIT was revealed only after operation, no significant differences were found (Tab 4). AIT therefore does not improve the clinical course of PTC patients.

Tab. 1 „Better" prognostic indicators of PTC associated to AIT

	PTC with AIT	PTC without AIT	Statistical significance
T1	63 %	**51 %**	0,0001
T2	16,2 %	**22,4 %**	0,008
T3	13,3 %	**16,4 %**	NS
T4	7,5 %	**10,2 %**	NS
distant mts	2,8 %	**5,9 %**	0,016

Tab. 2 „Better" prognostic indicators of PTC associated to AIT

	without AIT	with AIT
Microcarcinomas	16, 7 %	24,6%
Cumulative dose of ^{131}I	375 mCi	284 mCi
Remission till 5 years	84 %	92,3%
Persistence after 5 years	16 %	7,7%

Tab. 3 PTC prognostic indicators in patients with known AIT and AIT revealed only after TTE

	AIT known before dg. of PTC (65 % pts.)	AIT revealed only after TTE (35 % pts.)	Statistical significance
T1	68,2 %	53,6 %	0,0014
T2	14,8 %	18,5 %	NS
T3	10,4 %	18,5 %	0,012
T4	6,6 %	9,5 %	NS
distant mts	0,94 %	5,9 %	0,0035

Tab. 4 Comparison of prognostic indicators

	Without AIT	AIT revealed after TTE	Statistical significance
T1	51 %	53,6 %	NS
T2	22,4 %	18,5 %	NS
T3	16,4 %	18,5 %	NS
T4	10,2 %	9,5 %	NS
distant mts	5,9 %	5,9 %	NS

Conclusions:

We detected a high incidence of AIT in PTC patients. These data support the hypothesis that AIT is a predisposing factor in the development of PTC. Clinicians should pay particular attention to thyroid nodules in AIT, because it is a stronger predictor for PTC than other risk factors. We recommend a close observation for neoplastic changes in AIT patients.
AIT does not represent a protective factor against spreading of PTC. At first sight better prognosis of PTC with coexisting AIT is not caused by immunological mechanisms, but by follow up of AIT patients and therefore early diagnosis of PTC.