Novel insights in ultrasound evaluation of thyroid gland in children with papillary thyroid carcinoma

Dominika Januś 1,2, Małgorzata Wójcik 1,2, Anna Kalicka-Kaspirczyk 1,2, Grażyna Drabik 3, Łukasz Wyrobek 4, Anna Wędrychowicz 1,2, Jerzy B. Starzyk 1,2

1 Department of Pediatric and Adolescent Endocrinology, Chair of Pediatrics, Institute of Pediatrics, Jagiellonian University Medical College, Krakow, Poland
2 Department of Pediatric and Adolescent Endocrinology, University Children Hospital in Krakow, Poland
3 Department of Clinical Immunology and Transplantation, Institute of Pediatrics, Jagiellonian University, Medical College, Krakow, Poland.
4 University Children Hospital, Department of Radiology, Krakow, Poland

Correspondence to: Dominika Januś, MD., PhD.
Department of Pediatric and Adolescent Endocrinology, Chair of Pediatrics Institute of Pediatrics, Jagiellonian University Medical College Wielicka St. 265, 30-663 Krakow, Poland.
TEL: +48 12 658 12 77; FAX: +48 12 658 10 05; E-MAIL: dominika.janus@uj.edu.pl

Submitted: 2017-05-15 Accepted: 2017-09-15 Published online: 2017-10-18

Key words: autoimmune thyroiditis; papillary thyroid carcinoma; papillary thyroid microcarcinoma; ultrasonography of thyroid gland; normoechogenic thyroid

Abstract

BACKGROUND: The coincidence of autoimmune thyroiditis (AIT) in patients with papillary thyroid carcinoma (PTC) is ranging between 10 and 58% in the general population.
MATERIAL AND METHODS: In the present study retrospective ultrasound, clinical and autoimmune assessment of 24 patients diagnosed with papillary thyroid carcinoma between 2000–2016 was performed.
RESULTS: The coexistence of PTC and AIT was found in 50% of patients with PTC. Patients were divided into two groups. PTC AIT (+) group involved 12 children at the mean age 14.9 years (range 11–20 years, 9 girls) and PTC AIT (–) 12 children at the mean age 12.9 years (range 7–18 years, 5 girls). Papillary thyroid microcarcinoma (PTMC) was diagnosed in 6 patients (in 5 with AIT). US characteristics of PTC was heterogenous: hypoechogenic with/without increased vascularisation, normoechogenic with halo, with/without microcalcifications. In 70% PTC AIT (+) and in all PTC AIT (–) patients ultrasound analysis revealed that the thyroid tissue of the whole gland was normoechogenic. Local metastases in lymph nodes were found in 40% of PTMC AIT (+).
CONCLUSION: Lack of increased vascularization and microcalcifications and presence of ‘halo’ in the nodule does not exclude malignancy. Due to the presence of lymph node involvement in PTMC in all children with PTC total thyroidectomy should be performed with lymph nodes verification.

Abbreviations:
DTC - differentiated thyroid carcinoma
PTC - papillary thyroid carcinoma
PTMC - papillary thyroid microcarcinoma
AIT - autoimmune thyroiditis

AITD - autoimmune thyroid disease
FNAB - fine needle aspiration biopsy
aTPO - thyroperoxidase antibody
aTG - thyroglobulin antibody
TRab - TSH receptor antibody

PMID: 29106792  NEL380517A07 © 2017 Neuroendocrinology Letters • www.nel.edu
INTRODUCTION

Autoimmune thyroid disease (AITD) is the most common cause of acquired thyroid disease in pediatric patients (Zdraveska & Kocova 2012). The frequency of AITD is rising and has been reported between 0.3–2% in children and 4–9.6% in adolescents (Zois et al. 2003). Papillary thyroid carcinoma (PTC) accounts for 90% or more of all childhood differentiated thyroid carcinoma (DTC) cases (Niedziela et al. 2016). The prevalence of PTC, especially papillary thyroid microcarcinoma (PTMC) is rising in the last years partly due to more frequent ultrasound (US) assessments and US controlled fine needle aspiration biopsy (FNAB) of small nodules of the thyroid gland.

In the first report on the coincidence of thyroid cancer and AIT Dailey et al. (1955) postulated that AIT might be considered a precancerous lesion. Other researchers reported a coincidence of AIT in PTC ranging from 10–58% in the general population (Ott et al. 1985; Carson et al. 1996; Schaffler et al. 1998; Niedziela et al. 2006; Jankovic et al. 2013). In pediatric patients with DTC the coincidence of AIT is ranging from 6.3–43% depending on the patients selection (Danese et al. 1997; Corrias et al. 2008; O’Groman et al. 2010; Park et al. 2013; Iliadou et al. 2015). In a large case series presented by Corrias et al. (2008) thyroid nodules were found in 115 of 365 patients with AIT (31.5%), with 11/115 cases of PTC (9.6%). In a large study including 108 children Iliadou et al. (2015) have found that 28.6% of the patients with DTC (in 93.5 % with PTC) presented AIT.

In the last years there is an increase of coincidence of AIT and PTC. In adult patients with PTC, the prevalence of chronic lymphocytic thyroiditis increased four-fold in men and two-fold in women between 1999 and 2008 (Oh et al. 2014). In pediatric patients with PTC Niedziela et al. (2015) found that the prevalence of chronic lymphocytic thyroiditis increased ten-fold between 1996–2000 and 2001–2015 years.

According to the current pediatric guidelines neck US should be performed at least every 12 months in children with autoimmune thyroid disease (Niedziela et al. 2016).

The aim of the present study is ultrasound, clinical and autoimmune characterization of patients with papillary thyroid carcinoma.

SUBJECTS AND METHODS

Subjects

Retrospective analysis of medical records and thyroid ultrasound results of 24 patients diagnosed with PTC between 2000 and 2016 in the major tertiary pediatric endocrinology center was performed. The analysis included age at diagnosis, gender, the cause of referral to the endocrinologist, thyroid status (euthyroid, hypothyroid, hyperthyroid), levels of autoantibodies (aTPO assessed in 24 patients, aTG in 5 patients, TRab in 3 patients) and ultrasound features of the malignant nodule and the thyroid gland surrounding the nodule.

Postoperative staging was done based on the tumour, nodes and metastases (TNM) system proposed by the American Joint Committee on Cancer (Ito et al. 2010).

Patients were divided into two groups. PTC AIT (+) group involved 12 children at the mean age 14.9 years (range 11–20 years, 9 girls). PTC AIT (–) group involved 12 children at the mean age 12.9 years (range 7–18 years, 5 girls).

Methods

AITD was diagnosed based on clinical (presence of goiter, firm consistency of the thyroid gland), hormonal (hypothyroidism or thyreotoxicosis), typical features of chronic autoimmune thyroiditis on thyroid ultrasound assessment and increased aTPO, and/or aTG and/or TRab antibodies levels. AIT was diagnosed in euthyroid patients with an increased aTPO and/or aTG and/or TRab antibodies levels. PTMC was diagnosed after FNAB fulfilling Bethesda criteria (Cibas et al. 2009), and if on US assessment its diameter was ≤10 mm. In patients with PTC total thyroidectomy with lateral and central lymph nodes histopathological verification was performed.

The study was approved by the Institutional Review Board.

RESULTS

From 2000 to 2016 we had the total number of 24 cases of PTC in children treated in our center (Table 1). In the last two years an increase of newly diagnosed small PTC of diameter below 10 mm was observed, that may be associated with more frequent ultrasound assessment of patients in this time period, every 6 to 12 months (Table 1).

The coexistence of PTC with AIT was found in 50% (12/24) of patients and there was also an increase in the last two years (Table 1). In two patients: one AIT (+) and one AIT (–) PTC developed 7 and 13 years after prophylactic central nervous system irradiation due to acute lymphoblastic leukemia and in one patient AIT (–) 9 years after chest irradiation due to Wilms’ tumor (Table 1). In patient 11 PTC AIT (+) diabetes mellitus type 1 was diagnosed 5 years prior to PTC.

Thyroid status analysis of patients with PTC and AIT (+) at presentation found that 1 patient presented with thyrotoxicosis, 5 with subclinical (compensated hypothyroiditis) and 6 were euthyroid. 11 patients with PTC AIT (–) were euthyroid and 1 presented with compensated hypothyreosis (Table 1).

Analysis of the whole group of 24 PTC revealed that patients with PTC AIT (+) when compared to patients with PTC AIT (–) were older (14.9 vs 12.9 years, ns), females predominated (75% vs 41.6%), 5 micro PTC (41.6%) were detected (mean diameter 8.4 mm) vs. 1 microPTC in AIT (–) patients, the lymph node...
Ultrasound evaluation of thyroid gland involvement reached 58.3% (vs 91.6%), mean TSH (after excluding a patient with thyrotoxicosis at presentation) was higher (3.2 vs 2.3 uIU/ml). The cause of referral to the endocrinologist in PTC AIT (+) was a goiter in 7/12 (58.3%), a nodule found on ultrasound in 4/12 (33.3%) and in 1 patient lymph nodes enlargement (8.3%). In PTC AIT (−) the cause of referral was also a goiter in 7/12 (58.3%) patients, in 3/12 (25%) lymph nodes enlargement and a nodule found on US in 2/12 (16.7%). Three patients were referred to the hematologic unit first because of lymphadenopathy at presentation and the suspicion of Hodgkin lymphoma.

In patients with PTC AIT (+) the mean aTPO level assessed in 12 patients was 1823.6 IU/ml (range from 26.2-2726.6). The mean TSH level was 3.2 uIU/ml (range from 0.4-9.5). The mean TRAb level was 7.06 IU/l (range from 0.02-32.1). The mean aTG level was 2.41 IU/l (range from 0.64-7.7). The mean fT3 level was 15.5 pmol/l (range from 3.44-4.28). The mean fT4 level was 10.6 pmol/l (range from 1.2-20.2).

In patients with PTC AIT (−) the mean aTPO level assessed in 12 patients was 126.2 IU/ml (range from 26.2-726.6). The mean TSH level was 2.3 uIU/ml (range from 0.4-9.5). The mean TRAb level was 5.72 IU/l (range from 0.64-5.2). The mean aTG level was 7.06 IU/l (range from 0.02-32.1). The mean fT3 level was 10.6 pmol/l (range from 3.44-4.28). The mean fT4 level was 10.6 pmol/l (range from 1.2-20.2).

Tab. 1. Clinical characterisation of patients.

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>Cause of referral</th>
<th>Thyroid US PTC(mm)</th>
<th>TNM</th>
<th>PTC variant</th>
<th>131 J therapy</th>
<th>aTPO IU/ml N&lt;30</th>
<th>aTG U/ml N&lt;30</th>
<th>TRAb IU/l N&lt;1</th>
<th>TSH UIU/ml N:0.4-4.0</th>
<th>fT3 pmol/l N:3.6-8.6</th>
<th>fT4 pmol/l N:10-25</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 Goiter 20</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>+</td>
<td>70.7</td>
<td>2.41</td>
<td>7.06</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20 US 10</td>
<td>PT1aN1bM0</td>
<td>classic</td>
<td>+</td>
<td>722.5</td>
<td>0.64</td>
<td>5.72</td>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15 Goiter 15x20</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>+</td>
<td>1828</td>
<td>4.71</td>
<td>13.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13 Goiter 31x39</td>
<td>PT2N1bM1</td>
<td>classic</td>
<td>+</td>
<td>726.6</td>
<td>3.21</td>
<td>5.4</td>
<td>17.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18 Goiter 13</td>
<td>pT1bN0M0</td>
<td>classic</td>
<td>+</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>5.2</td>
<td>0.02</td>
<td>13.4</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17 US 21x16x26</td>
<td>PT2N1bM0</td>
<td>follicular</td>
<td>+</td>
<td>853.4</td>
<td>0.7</td>
<td>1.02</td>
<td>16.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>13 Lymph node enlargement 23</td>
<td>PT3N1bM1</td>
<td>diffuse sclerosing</td>
<td>+</td>
<td>&gt;9000</td>
<td>1.2</td>
<td>4.12</td>
<td>5.4</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>13 Goiter 8x8x9</td>
<td>PT1aN1aM0</td>
<td>classic/follicular</td>
<td>+</td>
<td>126.2</td>
<td>154.3</td>
<td>5.05</td>
<td>7.1</td>
<td>20.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>14 USG 7 and 2</td>
<td>PT1aN0M0</td>
<td>7 mm-classic/solid 2 mm-follicular</td>
<td>-</td>
<td>1300</td>
<td>4.8</td>
<td>1.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>16 Goiter 6</td>
<td>PT1aN0M0</td>
<td>classic</td>
<td>-</td>
<td>5911.2</td>
<td>300</td>
<td>2.12</td>
<td>15.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>17 USG 10</td>
<td>pT1aN0M0</td>
<td>classic</td>
<td>-</td>
<td>1271.7</td>
<td>5.01</td>
<td>11.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>11 Goiter 12</td>
<td>pT1bN0M0</td>
<td>follicular with capsule</td>
<td>-</td>
<td>42.94</td>
<td>43.39</td>
<td>2.01</td>
<td>1.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIT (−)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>7 Goiter 30</td>
<td>PT2N1bM0</td>
<td>classic/diffuse 15.6</td>
<td>+</td>
<td>11.6</td>
<td>1.83</td>
<td>6.9</td>
<td>12.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>16 USG n.a.</td>
<td>PT1bN1bM0</td>
<td>classic</td>
<td>+</td>
<td>-</td>
<td>1.44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>16 Goiter 17</td>
<td>PT2N0Mx</td>
<td>classic</td>
<td>+</td>
<td>-</td>
<td>2.4</td>
<td>13.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>18 Goiter 12x18</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>+</td>
<td>-</td>
<td>3.44</td>
<td>4.7</td>
<td>9.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>14 Lymph nodes enlargement 15x25</td>
<td>PT2N1bM0</td>
<td>follicular</td>
<td>+</td>
<td>15.7</td>
<td>2.05</td>
<td>4.8</td>
<td>19.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>17 Goiter 20x20</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>+</td>
<td>26.2</td>
<td>2.1</td>
<td>5.8</td>
<td>17.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>7 Goiter 13x11.5x21</td>
<td>PT2N1bM0</td>
<td>diffuse sclerosing</td>
<td>+</td>
<td>17.2</td>
<td>4.28</td>
<td>6.4</td>
<td>13.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>12 Lymph nodes enlargement 60x40</td>
<td>PT3N1bMx</td>
<td>classic</td>
<td>+</td>
<td>15.1</td>
<td>2.6</td>
<td>15.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>14 Goiter 12x13.1x17.6</td>
<td>PT1bN1bMx</td>
<td>classic / follicular</td>
<td>+</td>
<td>-</td>
<td>3.03</td>
<td>5.79</td>
<td>11.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>10 Lymph nodes enlargement 40</td>
<td>PT3N1bMx</td>
<td>solid with focus of anaplastic dedifferentiation</td>
<td>+</td>
<td>-</td>
<td>0.6</td>
<td>3.9</td>
<td>16.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>15 USG 13x7</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>+ &lt;30</td>
<td>&lt;20</td>
<td>1.7</td>
<td>4.1</td>
<td>1.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>9 Goiter 8x7.5x11</td>
<td>PT1bN1bM0</td>
<td>follicular</td>
<td>-</td>
<td>&lt;5.5</td>
<td>27.7</td>
<td>-</td>
<td>2.9</td>
<td>5.8</td>
<td>15.5</td>
<td></td>
</tr>
</tbody>
</table>
<30 to >9000), mean aTg assessed in 5 patients was 1703.5 U/ml (range<20 to >8000) and TRAb level assessed in 3 patients was 2.4 IU/l (range 0.7–5.2). The highest unmeasurable levels of aTPO >9000 IU/ml and aTG >8000 U/ml were found in a patient with diffuse sclerosing variant of PTC (Table 1).

In PTC AIT (+) we have been able to retrospectively assess thyroid ultrasound images of 10 out of 12 patients (83.3%). In 7/10 (70%) hypoechogenic PTC lesions were found (patients: 2,4,5,6,8,9,10), in 2/10 normoechogenic with hypoechogenic ‘halo’ (patients: 11,12) and in 1 patient with diffuse sclerosing PTC variant disseminated hyperechogenic lesions in the whole thyroid gland were found (patient 7). In 7/10 images no microcalcifications were visible on ultrasound images (2,6,10,8,9,11,12) and in 2/10 no increased vascularisation of the nodule was seen (patients: 8,9) (Figure 1).

In PTC AIT (–) patients we have been able to assess thyroid ultrasound images of 8 out of 12 patients (66.7%). In 4/8 irregular hypoechogenic PTC lesions with microcalcifications were found (patients: 13,18,20,21), in 2/8 normo/hypoechogenic with hypoechogenic ‘halo’ without microcalcifications (patients:16,24) and in 1/8 hypoechogenic without microcalcifications (patient: 23). In patient 19 diffuse sclerosing PTC variant was confirmed after histopathology. In all except one lesion increased vascularisation was found (patient 23). In patient 22 CT scan was performed due to neck lymph node enlargement and Hodgkin lymphoma suspicion, histopathology of lymph node revealed PTC (Figure 2).

To summarise in 15/18 (83.3%) patients malignant nodule was found to be hypoechogenic on ultrasound imaging.

In 7/10 (70%) AIT (+) patients (2,6,8–12) ultrasound analysis revealed that the thyroid tissue of the whole gland was normoechogenic and in 4/7 of these patients (8,9,11,12) the thyroid tissue directly surrounding the PTC nodules (with diameter from 7 to 12 mm) was hyperechogenic forming like a ‘border’ limiting the cancer (Figure 1).

In all PTC AIT (–) patients thyroid tissue of the whole gland outside the PTC nodule was normoechogenic. In the majority of patients PTC lesion was invasive and the diameter was larger than in PTC AIT (+) (24.8 vs 15.9 mm, p<0.09).

In our series of patients uninodularity was more frequent than multinodularity (patient 9).

PTC was suspected after first FNAB in 16/24 (66.7%) patients (1,3,5,6,8,9,11,13,14,16,17,18,19,20,21,23). PTC was suspected after second FNAB in one patient (4, 4.2%). PTC was suspected after third FNAB in two patients (2,24;8.3%).

**Fig. 1.** Ultrasound features of PTC in AIT(+) patients.
PTC was found after histopathological evaluation of removed thyroid gland in patients: 10 and 12 (8.3%). In patient 10 total thyroidectomy was performed due to large goiter (volume 55 ml) causing dyspnea and multinodularity (FNAB was benign twice). In patient 12 FNAB was benign twice, total thyroidectomy was performed due to multinodularity and increased diameter of nodules.

PTC was found in removed lymph node due to Hodgkin lymphoma suspicion in patients: 7,15,22 (12.5%).

Following PTC variants were found: 13/24 (54.2%) – classic (in 3 patients also with other components: diffuse sclerosing, solid, clear cell, follicular), 8/24 (33.3%) – follicular, 2/24 (8.3%) diffuse sclerosing and 1 patient – solid with anaplastic dedifferentiation (Table 1). Histopathology revealed that above mentioned hyperechogetic border of PTMC seen on ultrasound was formed by fibrotic tissue, microcalcifications and foci of lymphocytic infiltration (patients 8,9,11,12) (Figure 3).

In PTC AIT (+) patients local metastases in neck lymph nodes were found in 7/12 patients (58.3%), in
two also in the lungs and mediastinum. In 2/5 PTMC (40%) metastases in lymph nodes were found including one patient with microPTC of 9 x 8 x 8 mm dimensions with metastases found in as many as in 13/29 of lymph nodes assessed. In PTC AIT (−) patients local metastases in lymph nodes were found in 11/12 (91.7%).

Three patients PTC AIT (+) PT1aN0M0 (patients 9,10,11) and one patient PTC AIT (−) PT1bN0M0 (patient 24) were not treated with 131I therapy.

**DISCUSSION**

In this study, we presented the clinical and ultrasound characteristics of 24 pediatric patients with PTC with or without coincidence of autoimmune thyroiditis. The main cause of referral to the endocrinologist was a goiter in both groups. In 50% of patients autoimmune thyroiditis was diagnosed on the basis of a presence of an increased aTPO, aTG or TRab levels in serum. No PTC AIT (+) patient presented with an overt hypothyroiditis, 50% were euthyroid and in 50% AITD was diagnosed (41.7% presented with compensated hypothyroiditis and one with hyperthyroiditis). Ultrasound analysis of the thyroid gland provided further useful diagnostic information. Among patients with thyroid cancer, lymphocytic malignant nodules predominated (83%) over other ultrasound patterns. Whereas typically inAIT orAITD ultrasound imaging reveals hypoechoic thyroid gland due to more or less advanced lymphocytic infiltration that can be diffuse or focal, in our PTC cohort we observed that on ultrasound imaging inflammatory process in patients with PTC was not very advanced (Januś et al. 2017). In 70% PTC AIT (+) patients ultrasound analysis revealed that the thyroid tissue of the whole gland was normoechogenic and in 57.1% of these cases the thyroid tissue directly surrounding the PTC nodule was hyperechogenic forming like a `capsule/border’ limiting the cancer. Histologically, in above mentioned cases, fibrosis, microcalcifications and foci of lymphocytic infiltration were found in this tissue. The question arises then if in these patients autoimmune thyroiditis is not secondary to the cancer. These data are supported by Paparodis et al. (2014) reports that the form ofAITD pathology (destructive with clinically overt hypothyroiditis vs. a less-destructive with clinically compensated hypothyroiditis or euthyroid) may play a role in differentiated thyroid cancer risk. Patients with less destructive AITD were described to have a higher risk for differentiated thyroid cancer than patients with destructive AITD (Paparodis et al. 2014). These observations could provide a support for the hypothesis that autoimmune thyroiditis might be a secondary event (Januś et al. 2017).

According to Noureldine et al. (2015), recognition ofAITD as a precursor or a risk factor for thyroid cancer in pediatric population, would have a high clinical impact, given that Hashimoto’s thyroiditis is not rare and its incidence is rising in children (Ehlers & Schott 2014; Oh et al. 2014; Noureldine & Tufano 2015). It remains controversial whether autoimmune thyroiditis in children is a risk factor for developing PTC, is an incidental concurrent finding, or is a part of the host-tumor response system (Ehlers & Schott 2014; Noureldine & Tufano 2015).

Studies suggest that similar molecular mechanisms may influence early stages of oncogenesis and inflammation in the thyroid gland (Ehlers & Schott 2014; Noureldine & Tufano 2015). As presented by Ehlers et al. (2014) TG and TPO represent the main target antigens for cellular cytotoxic as well as humoral immune reactions (Ehlers & Schott 2014; Noureldine & Tufano 2015). In addition to Paparodis et al. (2014) study presenting that elevated anti-TPO antibodies appear to protect against thyroid cancer in patients with HT we would like to highlight the diffuse sclerosing variant of PTC with local and distant metastases where we have found unmeasurable high values of both aTPO and aTG levels. As presented by Ehlers et al. (2014) tumor-protecting feature of TPO might be explained by (a) complement-mediated cell death, that is anti-TPO antibody-dependent because anti-Tg antibodies do not fix complement (Weetman 2004; Ehlers & Schott 2014), and (b) anti-TPO antibody-dependent cell toxicity due to the exclusive binding of anti-TPO antibodies to their effector cells via Fc-g receptor I (CD64) that is known to be expressed on monocytes (Rebuffat et al. 2008; Ehlers & Schott 2014).

By contrast, aTG seem to represent a risk factor for PTC (Grani et al. 2013; Ehlers & Schott 2014; Vasiliedis et al. 2014). One reason for this effect could be the fact that aTG from PTC patients recognize different TG epitopes than do aTG from patients with autoimmune thyroid diseases (HT and Graves’ disease) and from PTC patients with associated thyroiditis (Latrofa et al. 2008; Ehlers & Schott 2014).

By analogy to autoimmune thyroiditis, TPO and TG also seem to represent the specific target antigens for the immune response in PTC (Ehlers & Schott 2014; Noureldine & Tufano 2015). Whether PTC develops despite autoimmunity or due to inflammation and preexisting autoimmunity, or whether AIT develops because of cross-reacting antitumor immunity, needs further research in pediatrics (Ehlers & Schott 2014).

From pathological perspective, it is important to distinguish between diffuse lymphocytic infiltration and focal peritumoral lymphocytic thyroiditis (Noureldine & Tufano, 2015). Hashimoto’s thyroiditis is a diffuse lymphocytic infiltration; therefore, it is considered an independent chronic process and does not signify a reaction to the tumor (Ehlers & Schott 2014; Noureldine & Tufano 2015). The reactive alterations of stromal cells caused by the chronic inflammation may lead to cellular damage, thereby resulting in tumor development (Buyukasik et al. 2011; Noureldine & Tufano 2015). The reason for the induced antitumor immune
response might be the existence of yet undiagnosed papillary thyroid microcarcinomas (PTMC) (Ehlers & Schott 2014). In our study ultrasound imaging in 4 patients PTC AIT (+), 3 of them with PTMC, is in favour for the latter category of the infiltration taking into account that the thyroid was normoechogenic and the direct tissue surrounding the nodule was hypoechogenic, ‘limiting’ the lesion, and could be a part of peritumoral lymphocytic infiltration with positive antibodies detected in serum. PTMC is considered as the earlier stage of disease which eventually evolves into PTC, potentially triggered by growth factors, as genetic studies revealed similar gene expression profiles in PTMC and PTC (Kim et al. 2010; Saranac et al. 2011). Possibly, these small malignancies induce a locally defined antitumor immune response (Ehlers & Schott 2014). This hypothesis certainly needs investigation in pediatric population.

Studies in adults have found that PTC patients with coexisting Hashimoto’s thyroiditis tend to display specific features (Dvorkin et al. 2013; Jara et al. 2013; Kwon et al. 2014; Zhang et al. 2014; Iliadou et al. 2015; Noureldine & Tufano 2015). They are likely to be young women, with less aggressive disease, less frequent nodal metastases, less likely to develop recurrence, and have a higher survival rate (Dvorkin et al. 2013; Jara et al. 2013; Kwon et al. 2014; Zhang et al. 2014; Iliadou et al. 2015; Noureldine & Tufano 2015). In children, in line with Iliadou et al. (2015) large pediatric study, we have also found that patients with PTC AIT (+) vs. PTC AIT (−) were older, females (75%) dominated and PTC nodules were smaller. Additionally in our study we have found PTMC in 41.6 % of cases of PTC AIT (+) and higher TSH levels, however without an overt hypothyroiditis. The earlier diagnosis of smaller PTC lesions in AIT (+) than in AIT (−) children was possible due to more frequent monitoring of patients with diagnosis of AITD or with AIT who are followed up with repeated US imaging (Iliadou et al. 2015).

In our PTC AIT (+) cohort we have also found local and distant metastases in the lymph nodes and in the lungs. Additionally what should be underlined is the fact that in 40% of PTMC AIT (+) metastases in lymph nodes were found including one patient with PTMC of 9 x 8 x 8 mm with metastases found in as many as 13/29 of lymph nodes assessed. Also in PTMC we observed one case of intrathyroidal invasion with multinodularity (both lesions as small as 7 and 2 mm). Therefore, in contrast to adult studies we are convinced that PTC and also PTMC in AIT (+) patients is not less aggressive disease than in AIT (−) pediatric patients (Iliadou et al. 2015). In Iliadou et al. (2015) pediatric PTMC study no better outcome of DTC was observed in regard to the absence or presence of AIT and additionally in patients with AIT and DTC more frequently invasive DTC with intrathyroidal infiltration and familial PTC were found. We are convinced that both in microPTC and macro PTC total thyroidectomy with lymph node verification should be performed in accordance to current recommendations (Niedziela et al. 2016). On the other hand in early detected nodules as small as 11, 10, 7 and 6 mm for the first time we did not find lymph node involvement what had an impact on the further therapy of our patients enabling the escape from 131I therapy.

A limitation of the present study is a small number of patients. Multi-center transition studies involving both pediatric and adult patients are needed to evaluate disease course and thyroid ultrasound data especially in the light of controversies regarding ultrasound evaluation of AIT patients. According to previous recommendations thyroid ultrasound scan in children with AIT as not changing the treatment, clinical course or outcome, should not be indicated routinely (de Vries et al. 2009) and according to current guidelines ultrasound assessment should be performed annually in children with AIT (Niedziela et al. 2016). Due to high coincidence of PTC with AIT in children we are positive that all patients with AIT should have thyroid ultrasound repeated at least annually to detect as small PTC as possible, before invasion to lymph nodes starts, thus enabling escape from 131I therapy, that stands in line with current recommendations (Niedziela et al. 2016, Januś et al. 2017).

**CONCLUSION**

Frequent coexistence of PTC and AIT underlines the need of ultrasound monitoring of patients with AIT and referral for FNAB if nodular goiter is detected. Patients with autoimmune thyroiditis – euthyroid with raised aTPO, aTG or TRab autoantibodies present in the serum as well as patients with AITD without overt hypothyroiditis in both cases with normoechogenic thyroid gland on US imaging should be followed up with at least annual US assessment.

The lack of microcalcifications or increased vascularity in a solid thyroid nodule is not a criterion of disqualifying from FNAB in children. All solid thyroid nodules should be referred for ultrasound verification in a tertiary thyroid department and finally referred for FNAB verification.

In patients with AIT the natural course of PTC and also microPTC is not less aggressive than in patients with PTC AIT (−). As in 40% of children with microPTC the metastases in lymph nodes were found in all children with PTC (micro and macroPTC) total thyroidectomy with lymph node verifications should be the treatment of choice.

**Authors’ contribution:** Study design: DJ. Study conduct: DJ. Data collection: DJ, AKK, AW, LW, GD. Data analysis: DJ, GD. Data interpretation: DJ, MW, GD, JS. Drafting manuscript: DJ, MW, JS. Revising manuscript content: DJ, MW, JS. Approving final version of manuscript: DJ, MW, JS. DJ takes responsibility for the integrity of the data analysis.

Authors' contribution: Study design: DJ. Study conduct: DJ. Data collection: DJ, AKK, AW, LW, GD. Data analysis: DJ, GD. Data interpretation: DJ, MW, GD, JS. Drafting manuscript: DJ, MW, JS. Revising manuscript content: DJ, MW, JS. Approving final version of manuscript: DJ, MW, JS. DJ takes responsibility for the integrity of the data analysis.
REFERENCES


