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Papillary thyroid cancer in three children

Rak brodawkowaty tarczycy u trojga dzieci

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Abstract

Introduction: Thyroid cancers (TC) are rare diseases in the pediatric population and represents 0.5–3% of all malignant tumors in children. Differentiated thyroid cancer (DTC) is a major TC in children. Every patient under 18 years of age diagnosed with a thyroid nodule should undergo a detailed medical examination. The screening test for children with an increased risk for DTC is ultrasound examination of the neck. Both ultrasound and clinical images of a tissue lesion are more important than its size. It should also be emphasized that autoimmune thyroiditis (AIT), a comorbid condition for TC, is increasingly often diagnosed in young patients. Because of the rare incidence of this kind of cancer, we present 3 case studies of patients with papillary thyroid carcinoma, hospitalized in the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of Developmental Age at Pomeranian Medical University (PMU) in Szczecin.

Key words:
autoimmune thyroiditis, thyroid cancer, papillary thyroid cancer.

Streszczenie

Wprowadzenie: Raki tarczycy (*thyroid cancers* – TC) są rzadką chorobą w wieku rozwojowym. Stanowią 0,5–3% wszystkich nowotworów złośliwych u dzieci. Zróżnicowany rak tarczycy (*differentiated thyroid cancer* – DTC) stanowi większość dziecięcych raków tarczycy. U wszystkich pacjentów poniżej 18. roku życia ze stwierdzonym guzkiem tarczycy należy przeprowadzić szczegółowy proces diagnostyczny. Badaniem przesiewowym u dzieci ze zwiększonym ryzykiem DTC jest ultrasonografia szyi. Obraz ultrasonograficzny zmiany oraz obraz kliniczny mają większe znaczenie aniżeli wielkość ogniska. Należy również podkreślić, że autoimmunologiczne zapalenie tarczycy, które może współwystępować z TC, coraz częściej diagnozuje się u młodych pacjentów. Ze względu na rzadkie występowanie tych nowotworów przedstawiono opis 3 przypadków raka brodawkowatego terczycy u pacjentek hospitalizowanych w Klinice Pediatrii, Endokrynologii, Diabetologii, Chorób Metabolicznych i Kardiologii Wieku Rozwojowego PUM w Szczecinie.

Słowa kluczowe:
rak tarczycy, rak brodawkowaty tarczycy, autoimmunologiczne zapalenie tarczycy.

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Introduction

Thyroid cancers (TC) are rare diseases in the paediatric population and represent 0.5-3% of all malignant tumours in children [1, 2]. Differentiated thyroid cancer (DTC) is a major TC in children [3]. New incidences of DTC in people under 19 years of age comprise 2.3% of all thyroid cancers (National Cancer Registry data from 2003–2013) [4]. In recent years there has been an increase in TC rates both in Poland and in the rest of the world. Epidemiologic studies indicate that the incidence of DTC in children and adults is increasing by 6.5% per year [5, 6] and is estimated to be 0.54 cases per 100,000 people [2, 7]. Unlike in adults, the majority of paediatric cases represent papillary thyroid cancer (PTC) in various histological variants, and account for around 90% of all cases of DTC in children [4]. In patients over 15 years of age, PTC is diagnosed 10–13 times more often than in children under 10 years old [8, 9]. Papillary thyroid cancer is the second most frequently diagnosed solid cancer in girls, and the eighth in boys [9, 4]. It does not clearly correlate with gender before adolescence. However, after adolescence, the ratio between the PTC incidence in males and females increases and is 3:1 (4:1 in adults) [1]. The risk of thyroid nodule cancer incidence in children is much higher in comparison to adults, i.e. 22–26.4% and 5–10%, respectively [9, 1]. In autonomic nodule cases, the risk is even higher, i.e. 30% in children [9, 10]. Some of the risk factors of TC incidence in children are radiotherapy due to other cancer, ionic radiation exposure (especially in children under five years of age), thyroid autoimmunological diseases, and some genetic diseases (familial adenomatous polyposis, Carney complex, Cowden disease, Werner syndrome, Beckwith-Wiedemann syndrome, familiar parangliomas, Li-Fraumeni syndrome) [4]. In Niedziela's papers, it is indicated that the risk factors for thyroid cancer are also age under 10 years and male gender [11]. It has also been noticed that there is a correlation of increased concentration of thyroid-stimulating hormone (TSH) with the risk for PTC [12].

The biology of PTC in children is different than in adults. It is worth emphasising that PTC has a very good prognosis after the application of optimal treatment, despite the fact that it is generally diagnosed at an advanced stage [1]. In comparison to adults, lymph node (LN) and lung metastases in children occur more often [2]. At the time of diagnosis LN metastases occur in 78% of all cases, and lung metastases in about 9% to 30% [1, 10]. Depending on the author, 10-year survival is from 80% to 98% [10, 13], and the risk of death due to TC in patients under 20 years of age is 0.1% [8]. The comorbidity PTC and autoimmune thyroiditis (AIT) has been observed. It is in the range 1.3% and 6.3% up to 50%, depending on the age of the patients and the author [13–15]. The prevalence of AIT is about 2% in children and 10% in young people [13, 15].

The connection between AIT and PTC has been observed for 50 years and is still a matter of debate. Some authors claim that the presence of AIT is beneficial for patients with TC; however, such data mainly concern adults [14].

Because of the rare prevalence of DTC in children we describe three cases of PTC in patients hospitalised in our clinic.

Case 1

Patient ER, female, 12 years of age. During her first year of life, the girl underwent closure of her patent ductus arteriosus. She had a negative family history of cancer and autoimmune diseases. At the age of 10 she was referred for medical examination to the Clinic of Endocrinology, due to subclinical hypothyroidism diagnosed one month earlier. At that time, she was treated with L-thyroxine 25 μg/d. The results of the first laboratory diagnostics were: TSH 3.56 uIU/ml [N: 0.60–4.84], FT4 1.46 ng/dl [N: 0.97–1.67], FT3 4.39 pg/ml [N: 2.53–5.22], anti-TPO antibodies (TPOAb) 41.49 IU/ml [N: 0.00–18.00], and anti-Tg antibodies 445.90 IU/ml (TgAb) [N: 0.00-37.00]. Hashimoto's thyroiditis was diagnosed. Ultrasound examination detected enlargement of the thyroid gland (right part 41 $\times$ 23 $\times$ 26 mm, left part 42 $\times$ 19 $\times$ 17 mm, isthmus 4 mm) with heterogeneous parenchyma and reduced echogenicity. In the right lobe, the scan revealed a few focal lesions, which were hyperechogenic in comparison to the surrounding parenchyma, with a diameter of up to 4 mm. Moreover, in the isthmus there was a change with a cyst morphology, 6 $\times$ 4 mm in size. No pathological lesions were diagnosed in the lymph nodes that were examined. Histopathological examination of the lesions of the right thyroid lobe material from the fine-needle aspiration biopsy (FNAB) detected a group of thyroid follicular cells with intranuclear grooves and vacuoles. The cytological image corresponded to a thyroid follicular lesion of undetermined significance, group III according to the Bethesda classification. After conversation with her parents, it was planned to perform a control thyroid ultrasound examination three months later and, following surgical consultation, finally enrol the girl for surgical treatment. The ultrasound performed in May 2017 showed a well-separated, normoechogenic, heterogeneous lesion with marginal vascularisation measuring 14 $\times$ 16 $\times$ 28 mm in the central part of the right thyroid lobe, but with 2 $\times$ 7 mm in the isthmus of the cyst. In June 2017 surgical removal of the right thyroid lobe was performed. The presence of an unevenly separated tumour, 24 mm in diameter, was macroscopically detected. Histopathological examination showed non-encapsulated focal points of PTCC (papillary thyroid carcinoma, classic variant) with the greatest dimension of 18 mm. Evident excess of the thyroid parenchyma was not detected. Angioinvasion was shown on the periphery of the tumour. Furthermore, there were attributes of Hashimoto's thyroiditis and small, dispersed focal points of PTC in the thyroid. In one out of the three lymph nodes there were cancer metastases limited to the lymph nodes, (pT1bN1MxLVI1; IHC: Ck19[+]). During the oncological case conference held in July 2017, re-surgery and supportive radioiodine therapy were advised. L-thyroxine was administered in a suppressive dose to obtain a TSH concentration in the range 0.1–0.4 μIU/ml. The removal of the isthmus and left lobe of the thyroid, as well as the pretracheal lymph nodes and mediastinal lymph nodes, were performed in October 2017. Histopathological examination showed thyroid cancer with chronic lymphocytic Hashimoto type inflammation, while metastases of PTC were detected in 10 out of the 33 lymph nodes. Angioinvasions were detected

in the blood vessels of the LN cavity and the LN capsules (in 10 out of 33 lymph nodes). Histopathological samples were consulted at the Department of Cancer Pathology of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Gliwice, where the diagnosis was confirmed. The patient was enrolled for radioiodine therapy, which was performed in February 2018 (ablation dose I^{131} 100 mCi). Since that time the child has been under the strict control of the Cancer Centre in Gliwice and our clinic. Her current therapy includes L-thyroxine 125 μg/d, control TSH 0.251 μIU/ml, thyroglobulin concentration 0.06 ng/ml [N: 3.50–77.00].

Case 2

Patient JB, female, 15 years of age. In her medical history there was an episode of bleeding to the central nervous system in the process of vascular malformation, which took place after embolisation (embolisation of arteriovenous haemangioma and aneurysm), performed twice in 2015. In March 2017 juvenile rheumatoid arthritis was diagnosed. During hospitalisation in the Department of Rheumatology, the examination was extended to diagnose the girl for other autoimmunological diseases. High titre of antithyroid antibodies (TPOAb 1244.5 IU/l, TgAb 661.9 IU/l) at TSH 5.89 μIU/ml (N: 0.510–4.300) was detected. L-thyroxine 25 μg/d was included in the therapy. Ultrasound examination of the thyroid revealed the presence of a focal circular, hypoechogenic lesion, 13 $\times$ 9.5 mm in diameter, without vascularity in the right lobe, as shown by the Doppler method. Echogenicity of the parenchyma of both lobes was irregular, with many hypoechogenic regions. The surrounding lymph nodes were described as normal, with preserved cavities and perihilar vascularity. FNAB of the change was performed. The cytological image was typical for the PTC, Bethesda system VI group. MRI examination of the neck showed a focal point, 10 mm in diameter, located in the dorsal part of the thyroid right lobe, more clearly visible after the administration of a contrast agent. At the dorsal edges of the thyroid lobes, lymph nodes with attributes suggesting cancer metastases were visualised. Their structures had dimensions 7 $\times$ 5 mm in the right lobe and 6 $\times$ 4 mm in the left lobe. Visibility was improved after the administration of a contrast agent. During an oncological case conference, the girl was enrolled for surgical treatment. In November 2017 total thyroidectomy with the removal of LN group VI was performed. In postoperative histopathological examination, the presence of a non-encapsulated tumour in the right lobe, 8.5 mm in diameter was confirmed. It was diagnosed as PTC. The cancer infiltrated the parenchyma and thyroid capsule, without crossing it, and without angioinvasion or infiltration of the nerve trunks. Four lymph nodes with metastases were diagnosed; the remaining 23 metastases were not confirmed (pT1aN1aM0). The histopathological samples were consulted at the Department of Cancer Pathology of the Maria Skłodowska-Curie Memorial Cancer Centre and the Institute of Oncology in Gliwice, where the diagnosis was confirmed. The patient was enrolled for radioiodine therapy, which was performed in February 2018 (ablation dose I^{131} 100mCi). Since that time the child has been under the strict control of the Centre of Oncology in Gliwice and our clinic. Her current therapy includes L-thyroxine 125 μg/d, control TSH 0.036 μIU/ml, and thyroglobulin concentration 0.15 ng/ml (N: 3.50–77.00).

Case 3

Patient IK, female, 16 years of age, with Klippel-Feil syndrome and Kabuki syndrome. The girl has a family history of Klippel-Feil syndrome and Kabuki syndrome in her brothers and sisters and PTC in her mother's sister. In April 2017, ultrasound examination of the thyroid revealed the presence of a well-separated nodule measuring 10 $\times$ 8 $\times$ 8 mm in the central part of the left lobe, moderately inhomogeneous, peripherally hypoechogenic, in the central part normoechogenic and hyperechogenic, with small calcifications. FNAB was performed; the result of the histopathological examination was not diagnostic (group I in the Bethesda system). Histopathological examination was performed again after three months, resulting in a cytological image suggesting PTC, Bethesda system group V (thyroid follicular cells, dispersed, grouped, and in small papillary structures with abundant eosinophilic cytoplasm and increased brighter regions in cell nuclei, with the presence of a few grooves and intranuclear vacuoles). In March 2018, after enrolment by an oncological commission, partial thyroidectomy was performed (left lobe, isthmus, trachea, and mediastinum lymph nodes). The presence of an unclearly separated nodule, 7 mm in diameter, was macroscopically confirmed in the thyroid tissue that was removed. Histopathological examination showed the presence of multifocal papillary cancer, and in the remaining part of the lobe there were a few smaller foci of PTC (classical and follicular) with diameters of up to 1 mm. Furthermore, metastases of PTC (mpT3 N1M1, Ck19[+], CD56–) were detected in 2 out of the 7 LN. After a repeated meeting of the oncological commission, the patient was enrolled for resurgery, which was performed in July 2018. In the macroscopic examination of the surgical material, a micronodular structure of the thyroid lobe was observed. In the histopathological diagnosis, thyroid cancer with chronic lymphocytic inflammation was demonstrated (IHC:Ck19; CD56; p63). The samples were consulted at the Department of Cancer Pathology of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Gliwice. PTC foci were detected in the left lobe, the biggest being 9 mm in diameter, infiltrating the thyroid capsule (without invading the muscles), angioinvasion (> 4 vessels) as well as metastases to two LN (pT1a[m]N1a). The patient was enrolled for radioiodine treatment under conditions stimulating rhTSH. Therapy was performed in October 2018 (ablation dose I^{131} 100 mCi). Specific marker accumulation was not confirmed in chest scintigraphy performed after I^{131} treatment. Since that time, the child has been under the strict control by the Cancer Centre in Gliwice and our clinic. Her current therapy includes L-thyroxine 150 μg/d, control TSH 0.199 μIU/ml, thyreoglobulin concentration < 0.040 ng/ml (N: 3.50–77.00).

Discussion

Thyroid cancers are rare diseases in the paediatric population. In the majority of cases the diagnosis is made by accident, during medical examination of thyroid abnormalities. In two of the described cases, ultrasound examination of the thyroid was done because of a diagnosis of autoimmune thyroiditis (AIT) with hypothyroidism. In the third patient standard ultrasound examination was performed because of the identified Klippel-Feil syndrome and Kabuki syndrome. In all the child patients, it was confirmed that they had focal lesions from 4 mm to 13 mm in size; therefore, they were enrolled for FNAB. In adult patients, tumour changes with a primary diameter ≤ 1 cm are considered low-risk cases. In children, the size of the tumour as an enrolment criterion for FNAB is controversial. Thyroid volume changes with age, and the dimensions of the focal lesion cannot be a prognostic marker for malignant phenotype [4].

Thyroid cancer in children takes a different course than in adults, which is why patients under 18 years of age and over 18 years of age have different recommendations [16]. Every thyroid nodule in children should undergo detailed diagnostics, more so than in adults, because the probability of cancer in that nodule is several times higher in children than in adults [11, 16]. The risk of TC in children, which after FNAB is diagnosed as Bethesda system group III or IV, is high, i.e. 28% and 58%, respectively. With reference to adult patients, the same risk is 5% to15% in group III and 15-30% in group IV. It is for this reason that in such cases surgical treatment is recommended in young patients [4, 9]. The risk of TC in children with Bethesda system group V and VI is 100%, whereas in adults it is 50% to 75% in group V and 97% to 99% in group VI [4, 16].

In patients with a diagnosis of autoimmune thyroiditis, special diagnostic alertness should be maintained if there is, for example, the risk of a small comorbid cancer (< 1 cm) that is difficult to palpate due to increased thyroid consistency [11]. As a result, it is recommended that patients with Hashimoto's disease have ultrasound screening of the thyroid at least once a year [4]. In all the cases described in the present paper, the size of the thyroid focal lesion in ultrasound examination was around 10 mm in diameter.

The relationship between PTC and AIT has been the subject of several studies aiming to establish whether the co-existence of AIT influences the clinical course, pathological features, and prognosis in PTC. The first findings on that subject were published in 1955 by Dailey [17]. The results of the studies analysing the connection between AIT and PTC were often contradictory. The studies were performed in nonhomogeneous groups of patients with various stages of the disease, different histopathological types of PTC, and across a broad range of ages. The definition criteria of AIT were also heterogeneous.

In the meta-analysis conducted by Lee *et al*. involving a group of 10,648 PTC cases, it was shown that AIT was substantially more frequent in patients with PTC, compared to patients with benign tumours [18]. Another meta-analysis of 71 articles (44,034 patients with PTC) also indicated the relationship between PTC and AIT [19]. Moreover, Niedziela *et al.* observed a clear increase in the co-existence of AIT and PTC in children and young people. In their study they showed that the frequency of the co-existence of PTC and AIT in 2001–2015 was 41.4%, i.e. 10 times more than in 1996–2000 [20]. In the review performed by Resende de Paiva *et al*., comprising 36 studies (64,628 patients from 13 countries) and published in 1955–2016, they showed the relationship between PTC and AIT. It was ascertained that the relative risk of Hashimoto's thyroiditis in patients with PTC was 2.36 (95% confidence interval [CI] 1.55-3.29, $p < 0.001$), and PTC among patients with AIT 1.40 (95% CI: 1.07–1.85, $p < 0.016$). However, such a relationship between AIT and papillary, medullary, and anaplastic TC was not shown [21]. It has been observed that there is a correlation between a higher concentration of TSH and the frequency of f PTC in patients with AIT and nodular goitre [22].

Many authors emphasise the importance of ultrasonographic features characteristic of TC, such as the presence of an individual solid lesion, hypoechogenicity of the focus, its irregular boundaries, the heterogeneous image of the lesion with increased central vascular flow, or the presence of microcalcifications [4, 11, 13]. In paediatric patients there were also observations of cases of PTC with diffused infiltration, enlargement of the occupied lobe, and the presence of the microcalcifications that are indications for obligatory FNAB enrolment [4]. One of the patients described here presented with a few focal lesions, which were hyperechogenic to the surrounding parenchyma, with a diameter of up to 4 mm, without centralisation of vascularisation and microcalcification. However, it is worth emphasising the importance of the progression of the lesion's size, visible in the control ultrasound examination performed after three months. In the second case, it was shown that the girl had a single, heterogeneous, well-separated lesion, peripherally hypoechogenic, while in the central part normoechogenic and hyperechogenic, with small calcifications. In the third patient, the study showed the presence of an individual focal round hypoechogenic lesion without vascularisation shown by the Doppler method and microcalcification.

In most paediatric cases of TC, metastases to regional lymph nodes are detected at the moment of diagnosis. In the cases presented here, increased lymph nodes were not detected by palpation. Moreover, pathological lesions were not detected in ultrasound examination of the lymph nodes, but MRI of the neck performed in one of the patients confirmed the presence of pathological LN. Histopathological studies of the post-surgical material revealed metastases to the lymph nodes in every girl. In children with a diagnosed PTC, the occurrence of distant metastases is frequently confirmed, but this was not observed in the patients presented here.

Every patient with a pre-surgical diagnosis of TC should undergo a total thyroidectomy. The rare prevalence of TC in the paediatric population and the young age of these patients are the reasons why the oncological commission exercises great caution when making the decision of whether to conduct total thyroidectomy. Nevertheless, many authors emphasise that the removal of only one thyroid lobe is among the highest risk factors of the recurrence of the disease. Recommendations include

the additional removal of the neck lymph nodes of the given anatomical compartment. During surgery, the visualisation of the recurrent laryngeal nerve is recommended. The operation should be performed by an experienced surgeon [2, 4].

The aforementioned findings were confirmed by the clinical course of the post-surgical period in two of the described patients, who required re-surgery. Complementary I^{131} therapy in children with DTC reduces the risk of relapse. The authors of the Polish recommendations claim that such treatment should be considered in every paediatric patient. It is only at the lowest stage of advancement of pT1aN0 that giving up isotope treatment can be considered [4].

According to the American Thyroid Association (ATA), in children, unlike in adults, enrolment should be considered very carefully because increased mortality has been observed in patients treated with I^{131} due to PTC in childhood, mainly because of the development of secondary cancers (e.g. CNS, nipple, lung, prostate, kidney, salivary gland, lymphoma, leukaemia). The risk increases with a dose of I^{131} exceeding 200–300 mCi; however, the literature describes a case of leukaemia after 85 mCi and lung cancer after 150 mCi [9]. The I^{131} therapy, similarly to post-surgical treatment, should be performed in specialised medical centres with appropriate experience.

All the patients described herein were enrolled for radioiodine therapy. Therapy was performed in the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Gliwice, and an ablation dose of I^{131} 100 mCi was applied with a concentration of TSH > 30 mIU/l.

Currently, under Polish regulations, all patients undergo L-thyroxine therapy in a suppressive dose to obtain a level of TSH between 0.1 and 0.4–0.5 mIU/ml. Thyreoglobulin concentration with a simultaneous measurement of anti- thyreoglobulin antibody concentration is thought to be a sensitive marker after treatment is completed. This has been confirmed by therapy outcomes. Moreover, ultrasound examination of the neck is recommended every 6–12 months in patients from the moderate- and high-risk group and once a year in children from the low-risk group [4]. In the patients described herein, abnormalities in the examinations mentioned above were not observed.

Conclusions

Detailed diagnostics should be performed in all patients under 18 years of age with a detected thyroid nodule. In children with an increased risk for DTC, ultrasound examination of the neck is performed for screening. The ultrasound image of the lesion and the clinical image are more important than the size of the lesion. It should also be emphasised that AIT, which is a comorbid condition for TC, is increasingly diagnosed in young patients.

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