# Papillary Carcinoma of Thyroid Gland in a Two-year-old Child

### Papilárny karcinóm štítnej žľazy u dvojročného dieťaťa

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#### Summary

Background: Thyroid nodules are less common among children than among adults. By contrast, thyroid nodules are more often malignant in childhood than in adulthood. In children, 26% of thyroid nodules are malignant, while in adults the corresponding value is 5-10%. Risk factors for developing thyroid nodules in children are female sex, post-pubertal age, previous or co-existing thyroid disease, previous irradiation of the neck, and a family history of thyroid disease. In children younger than 10 years, when no risk factors are present, the incidence rates are practically negligible. Case report: A two-year-old girl presented with a right thyroid mass. Laboratory evaluation revealed normal levels of triiodothyronine and thyroid-stimulating hormone. Thyroid ultrasonography revealed a  $4.8 \times 3.2 \times 2.5$  cm nonhomogenous nodule. The patient underwent right hemithyroidectomy. The pathology was consistent with papillary thyroid carcinoma; therefore, total thyroidectomy and selective neck dissection were performed. Conclusions: We report a very rare case of papillary thyroid carcinoma in a two-year-old child with no risk factors. The detection of a thyroid nodule in such a young child with no pre-disposing risk factors does not exclude the possibility of thyroid carcinoma and warrants careful evaluation and appropriate therapy.

#### Key words

papillary carcinoma - thyroid gland - children - epidemiology - diagnosis - treatment

#### Súhrn

Cieľ: Ochorenia štítnej žľazy u detí sú zriedkavé. Na rozdiel od prevalencie, malígne nádory sú častejšie u detí (26 % tyreopatií) v porovnaní s dospelými (5–10 % tyreopatií). K rizikovým faktorom ich vzniku patrí ženské pohlavie, postpubertálny vek, už existujúce ochorenie štítnej žľazy, predchádzajúce ožarovanie oblasti krku a pozitívna rodinná anamnéza tyreopatie. U detí mladších ako 10 rokov, bez prítomnosti rizikových faktorov, sa malígne nádory štítnej žľazy vyskytujú raritne. Kazuistika: Dvojročné zdravé dievčatko bolo prijaté na naše pracovisko pre uzol laloka štítnej žľazy vpravo. Hladina tyreoidálnych hormónov bola v norme. Ultrasonografické vyšetrenie opísalo nehomogénny uzol veľkosti 4,8 × 3,2 × 2,5 cm. Dieťa podstúpilo pravostrannú hemityreoidektómiu. Na základe výsledku histopatologického vyšetrenia, ktoré odhalilo papilárny karcinóm štítnej žľazy, bola následne vykonaná reoperácia v zmysle dokončenia tyreoidektómie a selektívna disekcia lymfatických uzlín krku. Záver: Prezentujeme veľmi vzácny prípad papilárneho karcinómu štítnej žľazy u dvojročného dieťaťa bez prítomnosti rizikových faktorov. Výskyt uzla štítnej žľazy u takto malých detí môže byť podmienený malignitou, preto vyžaduje podrobnú diagnostiku a vhodnú liečbu.

#### Kľúčové slová

papilárny karcinóm – štítna žľaza – detský vek – epidemiológia – diagnostika – liečba

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.



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Submitted/Obdržané: 3. 11. 2015 Accepted/Prijaté: 7. 12. 2015

http://dx.doi.org/10.14735/amko2016139

#### Introduction

Thyroid nodules are less common in children and adolescents and have a prevalence between 0.2% and 1.8%, whereas in adults it is around 4–7%. In contrast to prevalence, thyroid nodules are more often malignant in children than in adults. In children, 26% of thyroid nodules are malignant, while in adults the corresponding value is 5–10% [1]. Risk factors for developing thyroid nodules in children are female sex, post-pubertal age, previous or co-existing thyroid disease, previous irradiation of the neck, and a family history of thyroid disease [2,3].

We present a very rare case of papillary carcinoma of thyroid gland in a two--year-old child with no risk factors.

#### Case report

A two-year-old girl was referred to a pediatric endocrinologist by a pediatrician where she was evaluated for growing painless right thyroid mass of six weeks duration. No change in her appetite or weight had been noted. Her mother denied hoarseness, heat intolerance, changes in bowel habits, hair loss, difficulty swallowing, or prior radiation exposure of her daughter. Her medical history included a normal birth and was unremarkable. Her family history was not significant for thyroid diseases.

She had a visible swelling of the right lobe of her thyroid with a palpable nontender  $5 \times 3$  cm nodule. The thyroid moved with swallowing. No lymph

nodes were palpated. She had no lid lag or tongue fasciculations. Heart, lung, and abdominal examinations were normal. On neurological examination, she had normal deep tendon reflexes and no weakness.

The thyroid ultrasonography showed a large nonhomogenous  $4.8 \times 3.2 \times 2.5$  cm nodule in the right lobe, left lobe had normal echostructure with normal size of  $1.3 \times 0.9 \times 2.3$  cm.

Thyroid function tests revealed that her thyroid-stimulating hormone (TSH) was 2.234 mIU/L (reference range, 0.5–4.70 mIU/L; International System of Units (SI)), free thyroxine was 14.7 pmol/L (reference range, 10–23 pmol/L; SI), and her calcitonine was 3.6 pg/mL (reference range, < 10 pg/mL; SI). Her TSH receptor antibody was undetectable (< 6%). Her thyroid peroxidase antibody and thyroglobulin antibody were negative. Her thyroglobulin concentration was 37  $\mu$ g/L (reference range,  $\leq$  60  $\mu$ g/L; SI).

Correlation of clinical features, imaging results, and laboratory data led to the conclusion of an euthyroid solitary nodule and child was referred to Department of Otorhinolaryngology, Head and Neck Surgery, Comenius University, Jessenius Faculty of Medicine, University Hospital in Martin, Slovak Republic, for surgery. Subsequently, she underwent a surgical revision with peroperative excision of the thyroid nodule. No specific patterns of papillary thyroid carcinoma (PTC) were observed on peroperative frozen

section examination. Thus, based on the clinical and peroperative histological findings, right hemithyroidectomy was performed (Fig. 1-3). The final pathologic examination of thyroid nodule revealed follicular variant of papillary carcinoma with incomplete infiltration of thyroid capsule, without extrathyroidal or intravascular propagation of the tumour. Upon diagnosis of PTC, additional evaluation was conducted. Chest X-ray showed no evidence of metastatic disease. Approximately two weeks after her initial surgery, a complete thyroidectomy with selective lymph node dissection was performed (Fig. 4). The final pathology from the left thyroid completion thyroidectomy showed normofollicular tissue of thyroid gland, and PTC was not detected. No metastasis in lymph nodes was identified. The disease was staged as stage I (T4a N0 M0). Subsequently, she underwent 131 radioactive ablation.

Two years after thyroidectomy, thyroid scan showed no significant uptake in the thyroid bed or elsewhere in her body, and thyroglobulin concentration was < 1  $\mu$ g/L (reference range,  $\leq$  60  $\mu$ g/L; SI) consistent with remission. She is maintained on thyroid hormone replacement therapy for thyroidectomy and postablative hypothyroidism.

#### Discussion Epidemiology

Endocrine cancers are very rare in children, with thyroid cancer being the



Fig. 1. Right hemithyroidectomy.

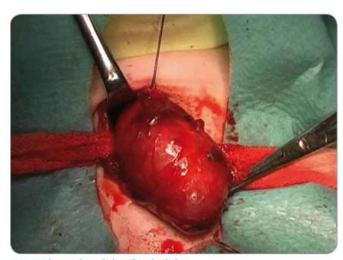
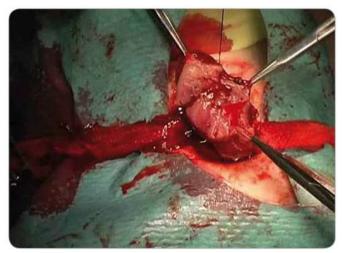


Fig. 2. Thyroid nodule of right lobe.



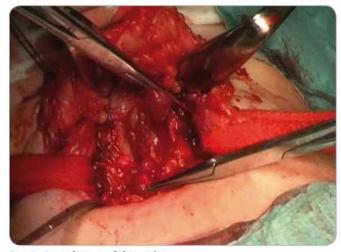


Fig. 3. Excision of thyroid nodule.

Fig. 4. Completion of thyroidectomy.

most common one constituting 0.5% to 3% of all childhood malignancies. The incidence in females is higher, with a 3:1 ratio before 15 years and 6:1 in the 15–19 year age group [4–6]. In very young children, incidence rates are practically negligible.

Thyroid carcinomas in childhood are almost always well differentiated. Recently, a multicentric study conducted on 120 pediatric patients with a thyroid nodule not associated with risk factors, such as autoimmune thyroid diseases or radiotherapy revealed a 16% occurrence of thyroid carcinoma, with 12% papillary, 2.5% follicular, and 1.7% medullary histotypes [7].

Familial occurrence for thyroid neoplasms is striking and well-documented for medullary thyroid cancer, and it is also frequently present in other histotypes [4]. Preexisting thyroid diseases represent a further risk factor. Cases of cancer have also been described in congenital hypothyroidism due to dyshormonogenesis, in iodide organification defects, in ectopy, as well as in thyroid hemiagenesis and thyroglossal duct cysts, usually of follicular histotypes [3].

Exposure to ionizing radiations is another well-known risk factor for thyroid cancer, especially for papillary carcinoma. Children's thyroid gland is much more sensitive to carcinogenic effects of ionizing radiation than that of adults. One explanation of this interesting biologic phenomenon is that

thyrocytes have a very low division rate at adult age compared to younger age groups. Radiation-induced mutations are thus less likely to be transmitted to later generations of cells in higher age groups in view of the early expiration of the potency of thyrocytes to divide [8.9].

Lower doses than those observed for most other radiation induced cancers may induce thyroid carcinogenesis (to the order of 0.10 Gy). High doses (>30 Gy) result in a lowered risk of thyroid cancer, probably due to cell killing [10]. From a historical viewpoint, the high incidence of thyroid cancers between 1940 and 1960 following the extensive use of low dose radiotherapy for benign pathologies of the head, neck, and chest like tinea capitis, scrofula, and an enlarged thymus is worth mentioning. In one of the earliest reports on this subject, Duffy et al. [11] showed how 35% of the pediatric patients with thyroid cancer had previously been irradiated for thymus enlargement.

A great deal of our knowledge about radiation effects on thyroid carcinogenesis arises from evidence from exposure to radioactive isotopes in the fallout from Chernobyl in April 1996. The relative incidence of thyroid cancer had increased from 0.1–0.3/100 000 before the accident to 3.3–13.5/100,000 in 1990–1996 [12]. Almost exclusively, a papillary histotype developed [13] that exhibited aggressive growth and early metastasis [14].

Nowadays, history of previous neck irradiation is obtained mostly in child-hood cancer survivors. The risk of thyroid cancer increases in parallel to radiation dosages of up to 20–29 Gy, but then falls at higher doses [10]. Furthermore, there is increasing evidence that chemotherapy might also be a causative factor [15].

There has been ongoing debate regarding the existence of distinct genetic alterations. Efforts have been made to identify acquired genetic abnormalities that will determine the tumour biological behavior and ultimately allow molecular prognostication. Most of the studies have been performed in radiation-exposed pediatric thyroid carcinoma, while most routine cases of thyroid cancer are indeed sporadic cases. New driver genes that are altered in radiation-exposed pediatric PTC cases have been identified. Nearly 84% had fusion of genes, most oncoproteins activate MAPK pathways, suggesting that pediatric PTC are also MAPK-driver cancer. Conversely, the prevalence of drive fusion oncogenes in sporadic pediatric PTC was much lower. Nearly 30% of cases are negative for fusion events and/or point mutations found in radiation-induced pediatric cohort [16,17]. As the risk factor for the development of sporadic pediatric thyroid carcinoma is not known and the landscape of sporadic pediatric cancer likely differs significantly from the landscape of the radiation-exposed

pediatric cases, it is expected that sporadic cases might have higher prevalence of point mutations than radiationinduced pediatric thyroid carcinomas.

In our case report, the child was a very young two-year-old girl, with no history of previous irradiation of the neck nor family history of thyroid disease. Papillary carcinoma developed in eufunctioning thyroid gland. Genetic investigation of thyroid tissue was not performed.

Considering the fact that this malignancy occurred in a two-year-old child, it can be hypothesized that so far unrecognized germinal mutations//tumor predisposition could initiate the disease. Therefore, the child is in secondary prevention program (not only to detect recurrence but event. also second primary tumor) and is followed by pediatric oncologist.

#### Differences in thyroid carcinoma between children and adults

Several studies have shown that thyroid carcinoma in pediatric patients differs from thyroid carcinoma in adults with respect to its presentation and its outcome. Compared with adults, thyroid cancers occurring in children are more aggressive, are discovered in advanced stages, and are associated with higher rates of recurrences [18–20].

Lymph node involvement at diagnosis is very frequent in children. Grisby et al. [19] reported a 29% incidence of cervical adenopathy clinically, but pathologically, 73% of patients had cervical lymph node disease. Similar results were observed by other authors [21,22]. Another common presenting sign is pulmonary metastases. The incidence of lung metastasis at presentation is reported to range from 6% to 33% [18,19,23]. It is noteworthy that no child with thyroid carcinoma reported in the literature has had bone metastasis at diagnosis. This is in contrast to the frequent occurrence of bone metastasis in adults [19]. Additionally, recurrence rates tend to be higher in children. Long-term follow-up data shows up to 30% of children with differentiated thyroid carcinoma have recurrent disease [24]. Significant

prognostic factors associated with the development of recurrent thyroid carcinoma, such as capsular invasion, soft tissue invasion, positive margins, and tumor location at diagnosis (thyroid only vs. thyroid and lymph nodes vs. thyroid, lymph nodes, and lung metastasis) were identified. In the study by Grisby et al. [19], none of the patients developed recurrent disease when the initial disease was confined to the thyroid. This was in contrast to a 50% recurrence rate in patients with thyroid and lymph node disease at diagnosis and a 29% recurrence rate in patients with thyroid, lymph node, and lung metastasis at diagnosis.

Taken together, thyroid carcinoma in pediatric patients tends to present with disease at a more advanced stage than adults. But, paradoxically, their overall survival rate is excellent.

Long-term follow-up data show 20-year survival rates of 90-99% for children with thyroid carcinoma [25,26]. The discrepancy between aggressive tumor presentation and excellent prognosis in children is not well explained. One suggestion is that this observation may be related to the nondiploid DNA content of the tumor. Zimmerman et al. [21] found that 25% of tumors in adults had nondiploid DNA compared with only 10% of tumors in children. Another suggestion for the difference in prognosis between children and adults is that thyroid tumors in children have a larger dependence on TSH. Therefore, TSH suppression with thyroid hormone replacement is a more effective treatment in children. In adults, over time, well differentiated thyroid carcinoma may dedifferentiate to poorly differentiated thyroid carcinoma, especially in the course of the development of metastatic disease. Children may have a better prognosis because of a lack of progression from well to poorly differentiated neoplasms [27].

## Management of thyroid nodules in children Diagnosis

Although thyroid cancer in children usually has very indolent course, even with pulmonary metastases, early diag-

nosis is important to identify patients as soon as possible who need to undergo surgery. The diagnostic steps for thyroid nodules in children and adolescents are similar to adults. In children, the traditional diagnostic approach to thyroid nodules consists of clinical, laboratory, and imaging evaluations. Risk factors for malignancy of thyroid nodules are a fast growing nodule, family history of thyroid carcinoma, previous neck irradiation, hoarseness, a very firm nodule, fixation of the nodule to adjacent structures, and cervical lymphadenopathy [1,3,28].

In the evaluation and management of nodular thyroid diseases, ultrasonography and fine needle aspiration biopsy (FNAB) are most important. Thyroid ultrasonography is the imaging method of choice for the evaluation of thyroid gland structure. Several ultrasound characteristics have been studied as potential predictors of thyroid malignancy. These characteristics are solid lesions, subcapsular nodule location, hypoechogenecity, microcalcifications, irregular margins, no halo, intranodular vascularity, and lesions of more height rather than width [29,30]. Sonographic features of associated lymph nodes also potentially increase the likelihood of malignancy, thus suggesting further diagnostic investigation. The ratio between the longitudinal and transversal axes of the lymph nodes below 1.5 (normally greater than 2), rounded profile of a lymph node, absence of hilum, presence of eccentric cortical thickening, nonhomogeneous pattern, and the increased vascular flow are other parameters commonly included as indicators of malignancy [31,32].

Furthermore, regular ultrasound screening should be performed in survivors of malignancy in childhood who received neck irradiation. After a first tumor in childhood, thyroid cancers are most likely to arise 6–7 years or more after the primary cancer, and the radiation-associated risk for thyroid cancer remains elevated for at least 20 years [33]. With these premises and considering that an early diagnosis might improve the outcome, it has recently been suggested to screen

the population of childhood cancer survivors who had previously undergone radiotherapy involving the head, neck or upper thorax by ultrasound [3].

In the last 30 years, FNAB has become a cornerstone in the evaluation of solitary thyroid nodules, cysts, and dominant nodules within multinodular goiters in adults. Fewer data are available in pediatrics given the consistently lower occurrence of the disease. Studies dealing with this issue recently [2,3] estimated its diagnostic accuracy as ranging from 75 to 95%, a value approximating that reported for adults.

The important question is whether FNAB is the most useful procedure to detect malignancy. In our experience, a biopsy is not always necessary as its diagnostic value is somehow limited due to false negative biopsy results, especially in the case of follicular histology [34,35], and might be too incriminatory in young children. From our experiences with adult and pediatric thyroidectomies, the indications for surgical revision were a dynamic change of a thyroid nodule, increase in size over time and signs of activation in laboratory values independent of histological confirmation.

In this case, a preoperative fine needle aspiration biopsy was not performed, and surgery was indicated according to the clinical, laboratory and ultrasonography findings.

#### Treatment

The primary treatment of thyroid nodules should be surgical. Thyroidectomy (total or hemithyroidectomy) is the most effective treatment modality of thyroid nodules in children and adults [28,36]. In management of solitary thyroid nodules, peroperative histopathologic investigation of thyroid nodule is a useful procedure that helps to distinguish benign from malignant pathology and modify the extent of the surgery - hemithyroidectomy vs. total thyroidectomy. Nonetheless, difficulties remain in distinguishing thyroid carcinoma from benign lesions, particularly in the case of follicular thyroid carcinoma vs. follicular adenoma or the follicular variant of PTC [37].

In our case report, according to results of peroperative histology that did not show structures of papillary carcinoma, hemithyroidectomy was indicated. Definitive histopathological investigation showed follicular variant of PTC; therefore, total thyroidectomy and selective lymph node dissection was performed.

The optimal management of children and adolescents is not well defined. Low treatment morbidity is a critical requirement of any strategy for this group of patients with an excellent prognosis and long life expectancy. Some investigators suggest that limited surgery that has lower incidence of complications, mainly permanent hypoparathyroidism, and subsequent thyroid hormone suppressive therapy are the most effective means of controlling this disease [21,24,38]. The majority of investigators recommend a combination of total thyroidectomy, selective lymph node dissection, postoperative 131 therapy, and thyroid hormone suppressive therapy [18,38]. Total thyroidectomy is a safe operation with low incidence of permanent nerve palsies or hypoparathyroidism when performed by experienced surgeon [19,28,36]. No complication was observed in our patient. Moreover, subsequent regular screening of thyroglobulin levels after total thyroidectomy helps to detect early recurrence of thyroid carcinoma.

#### Conclusion

Thyroid cancer comprises 0.5–3% of all childhood tumors and represents the most common head and neck malignant tumor in young people. Risk factors for developing thyroid nodules in children are female sex, post-pubertal age, previous or co-existing thyroid disease, previous irradiation of the neck, and a family history of thyroid disease. In children younger than 10 years, when no risk factors are present, the incidence rates are practically negligible.

We report a very rare case of PTC in a two-year-old child with no risk factors. The child was treated by total thyroidectomy and selective lymph node dissection. Postoperative <sup>131</sup>I therapy and

thyroid hormone suppressive therapy was administered. Our treatment recommendations are standard for all children and adolescents. Recurrence is common and lifelong follow-up is essential. Follow-up evaluation should rely on periodic physical examination, thyroglobulin measurements, and total body <sup>131</sup>l scintigrams.

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