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Case report

Long-term Follow-up of a Toddler with Papillary Thyroid Carcinoma: A Case Report with a Literature Review of Patients Under 5 Years of Age

Short Title: A toddler with papillary thyroid carcinoma

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What is already known on this topic?

Papillary thyroid carcinoma is the most common type of thyroid cancer; however, the frequency of PTC is extremely rare in children.

What this study adds?

This is the first case report of a long-term follow-up and successful outcome of papillary thyroid carcinoma in a patient under the age of two.

Abstract

Papillary thyroid cancer (PTC) is extremely rare in children. Herein, we present a case diagnosed with PTC at 15 months of age. We conducted a literature review of the published cases with PTC under five years of age. A $1^{3/12}$ -year-old male patient had initially presented with a complaint of progressively enlarging cervical mass that appeared four months ago. On physical examination, a mass located on the anterior cervical with the largest measuring 3x3cm was detected. Cervical and thyroid ultrasonography showed a 50x27 mm in size solid mass in the right lateral neck. Excisional biopsy revealed a follicular variant of PTC with capsular invasion. Subsequently, he underwent a complementary total thyroidectomy. He was diagnosed with intermediate-risk (T3N0M0) PTC. He developed permanent hypoparathyroidism. At the first year of the operation, he was treated with radioiodine ablation (RAI) since basal and stimulated thyroglobulin (Tg) levels tended to increase. Whole body scintigraphy was normal in the first year of RAI ablation. **On LT4 treatment, levels of TSH and Tg were adequately suppressed.** He is now $8^{6/12}$-year-old and disease-free on LT4 suppression therapy for seven years and three months. PTC has different biological behavior and a great prognosis compared to adults. The optimal treatment strategy for pediatric TC is total thyroidectomy, followed by RAI ablation. A regular follow-up with TSH suppression by thyroxin, serial thyroglobulin evaluation, and radioiodine scanning, when indicated, are the necessary follow-up procedures.

Keywords: Papillary carcinoma, Thyroid, Children

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Introduction

Differentiated thyroid carcinomas (DTC) are the most common endocrine malignancies in childhood. Papillary thyroid cancer (PTC) constitutes 1.4% of new childhood malignancies and 90% of DTCs (1). Notwithstanding thyroid carcinoma (TC) is rare in childhood, the incidence rate is increasing by 1.1% annually (2). Increased frequency of TC may be related to environmental factors or improvement in diagnostic scrutiny (3). Additionally, TC is the most frequently observed secondary malignancy in pediatric cancer survivors (4). Pediatric TC usually presents with neck masses or nodules without any accompanying symptoms. Furthermore, 60% of pediatric patients with PTC have regional lymph node metastases at diagnosis (5). Despite the aggressive course of TC in children compared to adults, it has an excellent prognosis in the pediatric population with 10-year and 30-year survival rates >95% and >98%, respectively (6,7,8). DTC is most frequently diagnosed in children between the ages of 11 and 17 (9,10). Although PTC is the most common type of TC, the frequency of PTC is extremely rare in children under five years of age. Herein, we report a one-year and three-month-old boy presenting with cervical mass who was finally diagnosed with PTC and compared his clinical findings with previously reported patients'.

Case report:

A $1^{3/12}$-year-old male patient initially presented with a complaint of progressively enlarging cervical mass noted four months ago. He was the second child of a healthy 30-year-old mother and a healthy 33-year-old father. There was no consanguinity, and he had a healthy sibling. Except for reactive airway disease, his past medical history was unremarkable without any radiation exposure, family history of TC, or other thyroid diseases. On physical examination, a mass located in the anterior region, measuring 3x3cm, was detected. His cardiovascular, respiratory, and abdominal physical examination findings were normal. Baseline laboratory analyses were within normal limits. Thyroid hormone levels were normal, and thyroid antibodies were negative. Cervical and thyroid ultrasonography showed a well-circumscribed solid mass with lobular contours in the right lateral neck, 50x27 mm in size. Chest X-ray and abdominal ultrasonography were normal. Subsequently, neck magnetic resonance imaging (MRI) was performed, which revealed a 5x3.5x3 cm mass lesion with well-circumscribed margins in the right thyroid lobe, extending into the upper mediastinum. T2-weighted MRI showed the T2 hyperintense lesion to have diffuse and intense enhancement after contrast material administration (**Figure 1).** Since imaging did not precisely identify the primary origin and allow a specific diagnosis to be made, with suspicion of a neck tumor with thyroid invasion, total excision of the cervical mass was performed. Macroscopic examination of the excision showed a well-circumscribed, solid, nodular lesion that is gray-white and measuring 4.5x3.5x3 cm in size. Hematoxylin-eosin stained sections of the lesion revealed follicular variant PTC (FVPTC) with capsular invasion. There was no vascular invasion or microscopic extra-thyroidal extension. On immunohistochemical evaluation, HBME-1 was found to be diffuse positive. Analysis of $BRAF^{V600E}$ mutation was negative. After the total excision of the cervical mass, technetium-99m thyroid scintigraphy showed a focus of activity in the middle of the neck. Subsequently, he

underwent complementary total thyroidectomy without prophylactic lymph node dissection since no metastatic lymph node was observed intraoperatively and on preoperative imaging. **In the postoperative period, serum level of calcium was 9.4 mg/dL [Normal range (NR): 8.4-10.4)], phosphorus: 5.3 mg/dL (NR:4-6.5), magnesium: 1.9 mg/dL (NR: 1.5-2.5), alkaline phosphatase: 136 U/L (NR: < 281), and PTH: 30 (15-65) pg/mL.** Vocal cord movements were normal, as well. Levothyroxine sodium (LT4) replacement (3.5 µg/kg/day) was initiated after the surgery. **Although serum calcium and PTH levels were normal postoperatively, during the follow-up, hypocalcemia developed due to delayed hypoparathyroidism (Calcium 5.1 mg/dL, phosphorus: 8.5 mg/dL, magnesium: 1.9 mg/dL alkaline phosphatase: 158 U/L, 25-OH vitamin D: 20.5 ng/mL and PTH: 7 pg/mL) and calcium carbonate and calcitriol replacement therapy were started 3 month after surgery.** Thyroglobulin (Tg) level was 1.3 ng/mL. The patient was categorized as Stage III (T3N0M0) and intermediate-risk with respect to tumor size and other clinical features (11). At the first year of the operation, basal and stimulated Tg levels tended to increase (Tg:3.8 ng/mL), and he was treated with 1 mCi/kg radioiodine ablation (RAI) following thyroxine hormone withdrawal and iodine-free diet. Before RAI therapy, thyroid stimulating hormone (TSH) was 86.8 mIU/L and stimulated Tg was 6.7 ng/mL. The patient did not show any adverse effects of RAI. Whole body scintigraphy (WBS) taken one week after radiation therapy yielded minimal thyroid remnant. Suppressive therapy with LT4 was restarted. Thyroglobulin levels were 2.8 ng/mL and 0.2 ng/mL, one month and two months after RAI ablation, respectively, and remained at low levels. WBS with a 5-mCi dose of I^{131} was normal, and the serum level of Tg was 0.7 ng/mL in the first year of RAI ablation. Our patient was examined and tested periodically every 3-6 months. A level of TSH between 0.1-0.5 mIU/L and a level of fT4 close to the upper limit were obtained. **Serum Tg levels of the patient remained below 0.04 ng/mL after the first year of RAI therapy.** Neck ultrasound was evaluated at 6-month intervals. With negative diagnostic results of the tests, our patient was accepted to be in remission, and he had no other metastatic foci. Since the patient developed permanent hypoparathyroidism, calcium and calcitriol supplements were continued.

At the recent evaluation, he was $8^{6/12}$-year-old with a height of 136.5 cm (0.8 SDS), a weight of 30 kg (1.3 SDS). His Tanner stage was I (testes volumes 2/2 mL). He is on thyroid hormone, calcium, and calcitriol supplementation. He is disease-free on LT4 suppression therapy for seven years and three months.

Research strategy and systematic review of literature

We conducted a systematic review of the published literature on PTC in patients under five years of age. We searched the literature from inception to May 2020, using the following keywords; 'papillary thyroid carcinoma' and 'differentiated thyroid carcinoma' filtered by age, including infant, toddler, and preschool child. Both searches were limited to the English

language. Up to date, only 10 patients with PTC younger than 5 years old have been reported (10,12-20). Clinical findings, histopathological features, and outcomes of the previous patients and the presented case are summarized in Table 1.

Discussion

The frequency of DTC increased in both children and adults over the decades. PTC is the most common type of DTC, which usually presents in the adolescent period with a female preponderance. Genetic predisposition, previous thyroid disease, history of malignancy, and radiation exposure are usually the underlying risk factors (21,22). The data on PTC in early childhood was limited to a few numbers of articles and case reports (8,10-18). Up to date, only 10 patients with PTC younger than five years of age have been reported. DTC displays female dominance in adolescence, whereas the female/male ratio is equal or slightly reversed under the age of ten years (3). Correspondingly, 6 out of 10 previously reported patients were male (10,12-14,17,18), and herein, we present a $1^{3/12}$-year-old male patient with FVPTC who was successfully treated with total thyroidectomy and RAI ablation.

Up to 70% of the initial manifestation of thyroid cancer is usually asymptomatic solitary neck mass with characteristically normal thyroid hormone levels. **Based on pathological examination, thyroid nodules in children are reported to have a higher incidence of malignancy than in adults (22%–26% and 5%–15% respectively) (23-25).** Large, hard, fixed, irregular nodules, male sex, being younger than ten years old, and cervical lymphadenopathy should be considered worrisome (22). Cervical mass was the initial finding in our case and previously reported patients, as well (10,12-20).

Patients with PTC should be questioned in terms of concomitant thyroid diseases (autoimmune thyroid disease, thyroid dysgenesis, dyshormonogenesis), environmental factors (iodine deficiency region), medical history of cancer, or neck radiation therapy, and family history of TC. Radiation exposure, family history of TC, or any other thyroid disease were negative in our patient. On the other hand, 3 out of 10 previously reported patients had a predisposition factor for PTC as follows: family history (n=1), congenital hypothyroidism (n=1), solitary hyperfunctioning nodule, and thyrotoxicosis (n=1) (10,18,20).

The classical diagnostic approach to thyroid nodules comprises evaluating TSH and T4 levels and thyroid ultrasonography. A fine-needle aspiration biopsy (FNA) should be performed for the nodules having highly suspicious features. Considering the probability of diagnostic delay due to inconclusive FNA that may occur owing to the very young age of the child, we preferred the excisional biopsy for our patient in the first place. TC in prepubertal children differentiates from adolescents and adults by exhibiting a more aggressive behavior pattern. Although prepubertal children appear to have more advanced disease with lymph node involvement and distant metastases or recurrent disease, they have a more favorable prognosis than adults (26). Correspondingly, our patient presented with an extensive cervical mass; he was diagnosed with Stage III PTC and classified as an intermediate-

risk group. However, he reached remission rapidly, and he had no recurrence in the seven-year follow-up. Nonetheless, the data on long-term outcome results in children under 5 years of age is inadequate (10,12-20).

FVPTC accounts for 22.5% of all PTC (27). According to adult studies, tumor size larger than 4 cm and the presence of local invasion are substantially associated with poor prognosis, whereas the behavior of well-encapsulated FVPTC is almost always indolent except for a few rare adult cases who had metastasis (27,28). Nonetheless, the data on prognosis regarding histologic subtypes of DTC are scarce in childhood (29). Similar to our patient, two girls under five years of age with FVPTC were reported previously (16,19). However, long term follow-up outcomes were not available in these patients.

Recently, genetic alterations were found to be associated with cancer predisposition and prognosis of TC. It is speculated that the distinct course of disease in childhood is associated with different genetic profiles. Point mutations in *BRAF* (B-Raf proto-oncogene), *TERT* (telomerase reverse transcriptase), *RAS* (rat sarcoma) genes are more frequent in adults, whereas *NTRK* (neurotrophic tyrosine kinase receptors) fusion oncogenes are seen at a high frequency in both children and adults (5,30,31) Additionally, *RET/PTC* rearrangements is the most common genetic alteration in childhood DTC which mainly occurs as a result of radiation exposure and is correlated with an aggressive course. Adult studies showed that *BRAF* mutations are related to poor prognosis and high risk of recurrence in PTC patients (32), while the impact of $BRAF^{V600E}$ mutation on the prognosis of childhood TC is not clear yet. Furthermore, a variety of genetic syndromes may increase the risk of PTC. The associated hereditary syndromes include familial adenomatous polyposis (*APC*), Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), Werner syndrome (*WRN*), Carney complex (*PRKAR1α*), and DICER1syndrome (*DICER1*) (33,34). Genetic alternations were investigated in only two out of 10 previously reported cases (12,17). One was positive for *RET/PTC* rearrangement, who presented with extensive lymph node involvement that extended into the mediastinum (12). Nevertheless, there was no radiation exposure in this case, and he was in remission for a 1.5-year follow-up period (12). The other patient was positive for *SQSTM1-NTRK3* fusion, who required targeted kinase inhibitors following surgery and RAI ablation (17). *BRAF* mutation status was tested in our patient and found to be wild type.

The optimal treatment strategy for pediatric TC is total thyroidectomy, followed by RAI ablation in the presence of indication. Neck dissection is recommended for cases with metastatic neck nodes, whereas prophylactic neck dissection is not advised for cases without clinical and radiological lymph node involvement (11). During operation, a rapid frozen section is considered to be beneficial in guiding management and cost-saving via reducing the need for a secondary operation (35). Our patient was treated with mass excision, followed by complementary total thyroidectomy. Owing to the patient's age, not having a locally invasive disease or distant metastasis, low Tg levels, and severe side effects of

therapy, RAI ablation was not primarily performed in the postoperative period. Observation with adequate TSH suppression was initially preferred. However, basal and stimulated Tg levels elevated in the first year of the surgery, albeit negative radiological progression, 1 mCi/kg radioiodine ablation (RAI) was performed. He has been on a TSH-suppressive dose of LT4 treatment for over seven years with no recurrence. Both total thyroidectomy and I^{131} RAI ablation have more complications in children than in adults (5,36). Transient/permanent hypoparathyroidism, recurrent laryngeal nerve damage, and postoperative bleeding/hematoma may occur. **Hypoparathyroidism after total thyroidectomy is seen more frequently in young children due to the fine and delicate structure, leading to damage to parathyroid glands (37). Other than younger age, central and bilateral lymph node dissection, Graves' disease, thyroid cancer, total thyroidectomy, and reoperation are also predictors of postoperative hypoparathyroidism (38,39). Recent studies suggest that along with the assessment of preoperative and postoperative calcium levels, measuring intraoperative PTH levels may be beneficial for anticipating the risk of postoperative hypocalcemia and the timing for parathyroid gland recovery (37,40).** Although no postoperative complications were seen in our patient as in reviewed patients, interestingly, he developed hypoparathyroidism in the third month of the surgery. In literature, this entity is defined as delayed hypoparathyroidism that can occur months and even years following thyroidectomy due to progressive atrophy of the parathyroid glands resulting in late-onset hypoparathyroidism (41,42). Secondary to RAI ablation, complications such as transient neck pain and edema, gastrointestinal symptoms, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eye, and nasolacrimal duct obstruction, secondary malignancies, pulmonary fibrosis may develop. However, RAI is accepted to be safe in children since the side-effects are dose-dependent (5,10). Furthermore, molecular targeted therapy has been demonstrated to be beneficial in children with PTC who have an advanced or refractory disease that is unamenable to RAI or further surgery (43). Mahajan et al. started targeted therapy (lenvatinib, subsequently switched to larotrectinib) for a five-year-old patient with NTRK3 fusion-positive metastatic PTC. They observed a clinical stabilization and no side effects during five months of therapy (17).

Patients with PTC require a regular follow up by testing serum Tg level and performing neck ultrasonography. Targeted TSH levels should be obtained. In addition, if the Tg level increases and thyroid USG is normal, a chest CT scan or a WBS should be performed. Our patient was followed up by a multidisciplinary team of pediatric endocrinologists, surgeons, pathologists, radiologists, nuclear medicine specialists. A collaborative approach is essential to maximize long term survival. Our patient has been examined and tested periodically every 3-6 months for over seven years. On the other hand, follow up strategy and long-term outcome results were not available in previously reported cases (10,12-20).

In conclusion, we present a one-year and three-month-old boy with FVPTC, who was successfully treated with total thyroidectomy, followed by RAI ablation. Previously, ten PTC patients under five years of age were reported while most of the patients' long-term outcome was unavailable. We observed over seven years of disease-free period in our patient. Our results could be a road map for clinicians dealing with this rare cancer in very young children.

Informed Consent: A written informed consent was obtained from the patient's family.

Authorship Contributions: Surgical and Medical Practices: Ayşe Pınar Öztürk, Esin Karakılıç Özturan, Feryal Gün Soysal, Seher Ünal, Göknur Işık, Gülçin Yegen, Semen Önder, Melek Yıldız, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler, Concept: Ayşe Pınar Öztürk, Design: Ayşe Pınar Öztürk, Data Collection or Processing: Ayşe Pınar Öztürk, Analysis or Interpretation: Ayşe Pınar Öztürk, Literature Search: Ayşe Pınar Öztürk, Writing: Ayşe Pınar Öztürk, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler

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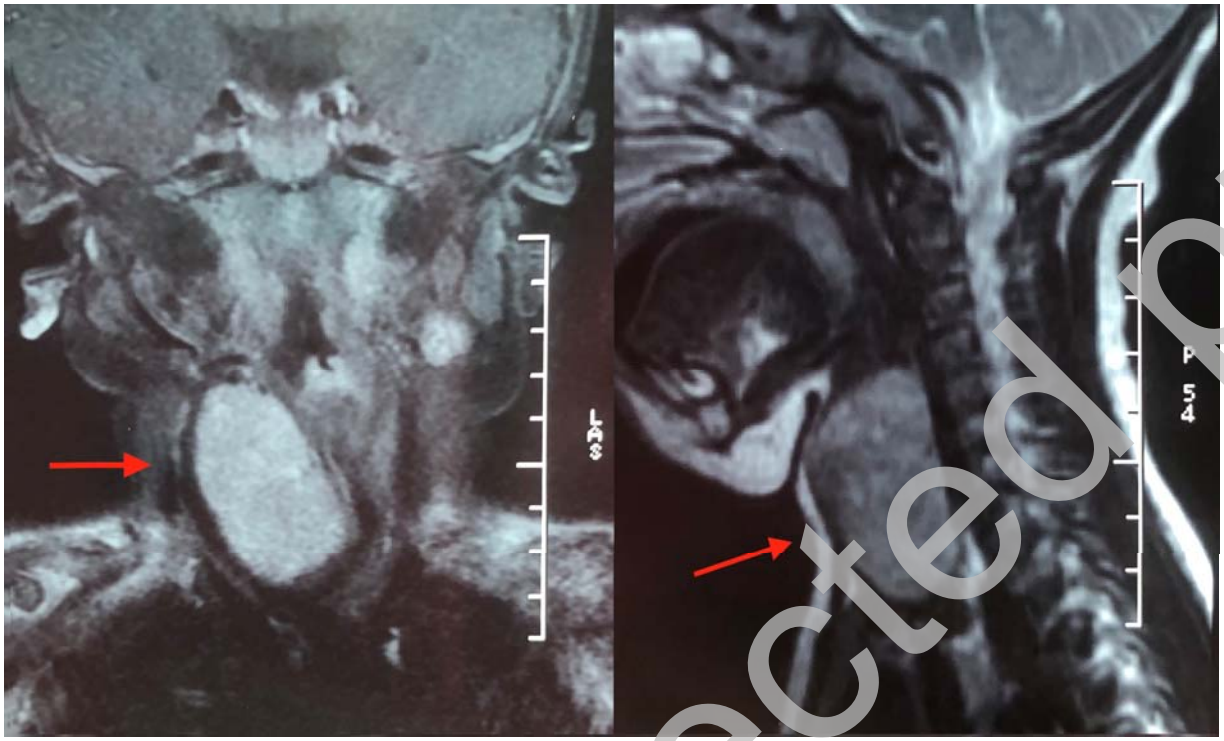

Figure 1. Coronal and sagittal planes, showing the mass lesion on MRI

Table 1. Clinical and genetic characteristics of patients under 5 years of age with papillary thyroid carcinoma

First author and year of publication	Age at diagnosis	Gender	Presenting symptom	Predisposing factor	Histopathological features	Capsule invasion/ LN involvement/ Metastasis	Genetic analysis	Treatment	Follow-up/ Outcome
Srikumar S., 2006	2 $^{8/12}$ year old	Male	Neck mass, 4.5 cm**	Negative	PTC	Negative	N/A	Near TT and RAI ablation	1 year/R
Alkan S., 2008	3 years	Male	Neck mass, 2x2 cm*	Negative	PTC	LN involvement	N/A	TT and BND, RAI ablation	N/A
Poddar S., 2008	11 months	Female	Neck mass, 1-1.5 cm**	Negative	PTC	Negative	N/A	Subtotal thyroidectomy and RAI ablation	2 months/NA
Khan MU., 2008	5 years	Female	Neck mass, 3x2.5x2.4 cm**	Negative	FVPTC	LN involvement	N/A	TT and selective right ND, RAI ablation	6 months/R
Drut R., 2009	5 years	Female	Thyroid nodule, 0.7 cm*	Congenital hypothyroidism	PTC	Capsule invasion/ LN involvement	N/A	TT and regional LND	N/A
Khara L., 2010	3 $^{5/12}$ year old	Male	Neck mass, 4x4 cm**	Family history of TC	PTC	LN involvement	N/A	TT and BND, RAI ablation	N/A
Damle N., 2011	5 years	Male	Neck mass, 3.4×2.2 ×2 cm**	Solitary hyperfunctioning nodule, thyrotoxicosis	PTC	N/A	N/A	TT	6 months/R
Gayathri BN., 2014	5 years	Male	Neck mass, 0.7x0.8x0.9 cm**	Negative	PTC	LN involvement positive	RET positivity	TT and BND, RAI ablation	1.5 years/R
Uhliarova B., 2016	2 years	Female	Neck mass, 5x3 cm*	Negative	FVPTC	Incomplete capsule invasion	N/A	TT and selective LND, RAI ablation	2 years/R

Mahajan P., 2018	5 years	Male	Neck mass, (size N/A)	Negative	PTC	Extensive LN and pulmonary involvement	SQSTM1-NTRK3 fusion positive, BRAF negative	Near TT, LND and resection of the bulky mediastinal component, RAI ablation and targeted therapy***	5 months/ Clinically stable
Presented case	$1^{3/12}$ -year-old	Male	Neck mass, 5x2.7 cm	Negative	FVPTC	Negative	BRAF negative	TT, RAI ablation	$7^{3/12}$ years/R

*BND, bilateral neck dissection; FVPTC, follicular variant papillary thyroid carcinoma LN, lymph node; LND, lymph node dissection; NA, not available; ND, neck dissection; PTC, papillary thyroid; carcinoma; R, remission; RAI, radioactive iodine; TC, thyroid carcinoma; TT, total thyroidectomy *On physical examination, ** On radiology, *** lenvatinib and larotrectinib*