CASE REPORT

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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

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What is already known on this topic?

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. However, the frequency of PTC is extremely low in children.

What this study adds?

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

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 1.25-year-old male patient had initially presented with a complaint of progressively enlarging cervical mass that appeared four months earlier. On physical examination, a mass located in the anterior cervical region with the largest measurements of around 3x3 cm was detected. Cervical and thyroid ultrasonography showed a 50x27 mm 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. In 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 levothyroxine sodium (LT4) treatment, levels of thyroid stimulating hormone (TSH) and Tg were adequately suppressed. He is now 8.5-years-old and disease-free on LT4 replacement therapy for seven years and three months. Pediatric PTC has different biological behavior and an excellent prognosis compared to adults. The optimal treatment strategy for pediatric TC is total thyroidectomy, followed by RAI ablation. Post-operative management should include regular follow-up, TSH suppression by adequate LT4 therapy, serial Tg evaluation, and radioiodine scanning when indicated.

Keywords: Papillary carcinoma, thyroid, children

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 that thyroid carcinoma (TC) is rare in childhood, the incidence rate is increasing by 1.1% annually in Europe. Increased frequency of TC may be related to environmental factors or improvement in diagnostic scrutiny (2). Additionally, TC is the most frequently observed secondary malignancy in pediatric cancer survivors. Pediatric TC usually presents

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with neck masses or nodules without any accompanying symptoms. Furthermore, 60% of pediatric patients with PTC have regional lymph node metastases at diagnosis (3). 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 >99% and >96%, respectively (4). DTC is most frequently diagnosed in children between the ages of 11 and 17 (5,6). Although PTC is the most common type of TC, the frequency of PTC is extremely low in children under five years of age. Herein, we report a one-year and three-month-old boy presenting with cervical mass, which was finally diagnosed as PTC, and compared his clinical findings with previously reports.

Case Report

A 1.25-year-old male patient initially presented with a complaint of progressively enlarging cervical mass, first noted four months earlier. 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, notably without any radiation exposure, family history of TC, or other thyroid diseases. On physical examination, a mass located in the anterior cervical region, measuring 3x3 cm, 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, 5x2.7 cm 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 was gray-white in color 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, Hector Battifora mesothelial epitope-1 was found to be diffusely positive. Analysis of $BRAF^{V600E}$ (The B-type Raf kinase) mutation was negative. After total excision of the cervical mass, technetium-^{99}m 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 had been observed intraoperatively or on preoperative imaging. In the postoperative period, serum calcium was 9.4 mg/dL [normal range (NR): 8.4-10.4], phosphorus was 5.3 mg/dL (NR: 4-6.5), magnesium was 1.9 mg/dL (NR: 1.5-2.5), alkaline phosphatase: 136 U/L (NR: <281), and parathyroid hormone (PTH) 30 (15-65) pg/mL. Vocal cord movements were normal. Levothyroxine sodium (LT4) replacement (3.5 µg/kg/day) was initiated after 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 three month after surgery. Basal thyroglobulin (Tg) level was 1.3 ng/mL. The patient was categorized as stage 3 (T3N0M0) and intermediate-risk with respect to tumor size and other clinical features (7). One year after the operation, stimulated Tg levels tended to increase up to 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, 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. Basal Tg 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.

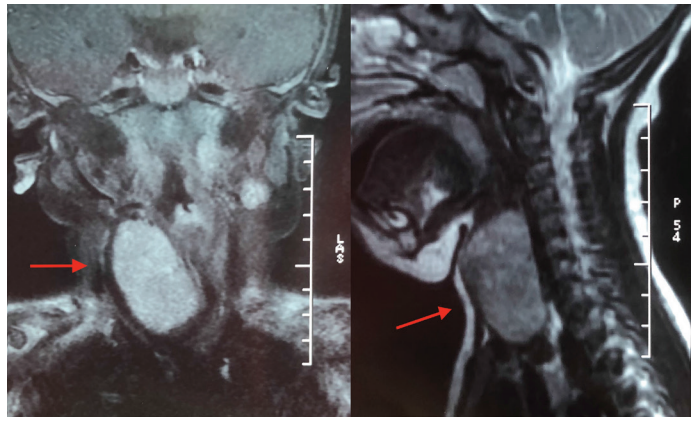

Figure 1. Coronal and sagittal planes, showing the mass lesion on magnetic resonance imaging

WBS with a 5 mCi dose of I^{131} was unremarkable with no remnant thyroid tissue, and the serum level of Tg was 0.7 ng/mL in the first year after RAI ablation. The 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 maintained. Serum Tg levels remained below 0.04 ng/mL after the first year of RAI therapy. Neck ultrasound was evaluated at 6-month intervals. Given these results, the patient was accepted to be in remission, and he had no evidence of other metastatic foci. Since the patient had developed permanent hypoparathyroidism, calcium and calcitriol supplements were continued.

At the most recent evaluation, he was 8.5-years-old with a height of 136.5 cm [0.8 standard deviation score (SDS)] and a weight of 30 kg (1.3 SDS), and his Tanner stage was 1 (testes volumes 2/2 mL). He is on LT4 (150 µg/day), calcium (50 mg/kg/day), and calcitriol (1 µg/day) supplementation and has been disease-free for seven years and three months.

Research Strategy and Systematic Review of Literature

A systematic review of the published literature on PTC in patients under five years of age was conducted. The literature was searched 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 ten patients with PTC younger than five years old have been reported (5,8,9,10,11,12,13,14,15,16). Clinical findings, histopathological features, and outcomes of the previous patients and the presented case are summarized in Table 1.

Discussion

The frequency of DTC has increased in both children and adults over the decades (3). 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 (17). The data on PTC in early childhood was limited to a few articles and case reports. DTC displays female dominance in adolescence, whereas the female/male ratio is equal or slightly reversed under ten years of age (3). Correspondingly, 6 out of 10 previously reported patients were male (5,8,9,10,13,14), and herein, we present a 1.25-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) (18). Large, hard, fixed, irregular nodules, male sex, being younger than ten years old, and cervical lymphadenopathy should be considered worrisome (19). Cervical mass was the initial finding in our case, as was the case in the previously reported patients (5,8,9,10,11,12,13,14,15,16).

Patients with PTC should be questioned about concomitant thyroid diseases, including autoimmune thyroid disease, and congenital hypothyroidism including thyroid dysgenesis and dyshormonogenesis, environmental factors (iodine deficiency region), medical history of cancer, or neck radiation therapy, and family history of TC. There was no indication of radiation exposure, family history of TC, or any other thyroid disease in our patient. In contrast, 3 out of 10 previously reported patients had a predisposition factor for PTC, including family history (n = 1), congenital hypothyroidism (n = 1), solitary hyperfunctioning nodule with thyrotoxicosis (n = 1) (5,14,16).

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 excisional biopsy for our patient in the first place. TC in prepubertal children is differentiated from TC in 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 (20). Correspondingly, our patient presented with an extensive cervical mass. He was diagnosed with stage 3 PTC and classified as an intermediate-risk group. However, he reached remission rapidly and has had no recurrence during the seven-year follow-up period. Nonetheless, the data on long-term outcome results in children under five years of age is scarce (5,8,9,10,11,12,13,14,15,16).

FVPTC accounts for 22.5% of all PTC. Based on findings from adult studies, tumor size larger than 4 cm and the presence of local invasion are closely associated with poor prognosis, whereas the behavior of well-encapsulated FVPTC is almost always indolent, except for a few rare adult cases in which there was metastasis (21). Nonetheless, the data on prognosis regarding histologic subtypes of DTC are scarce in childhood. Similar to our patient, two girls under five years of age with FVPTC were reported previously (12,15).

Table 1. Clinical and genetic characteristics of patients under 5 years of age with papillary thyroid carcinoma (5,8,9,10,11,12,13,14,15,16)

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 et al (10) 2006	2.67 years	Male	Neck mass, 4.5 cm**	Negative	PTC	Negative	N/A	Near TT and RAI ablation	1 year/R
Alkan et al (9) 2008	3 years	Male	Neck mass, 2x2 cm*	Negative	PTC	LN involvement	N/A	TT and BND, RAI ablation	N/A
Poddar et al (11), 2008	11 months	Female	Neck mass, 1-1.5 cm**	Negative	PTC	Negative	N/A	Subtotal thyroidectomy and RAI ablation	2 months/ NA
Khan et al (15) 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 and Moreno (16) 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 et al (5) 2010	3.42 years	Male	Neck mass, 4x4 cm**	Family history of TC	PTC	LN involvement	N/A	TT and BND, RAI ablation	N/A
Damle et al (14) 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 et al (8) 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 and Hajtman (12) 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 et al (13) 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	1.25-years	Male	Neck mass, 5x2.7 cm	Negative	FVPTC	Negative	BRAF negative	TT, RAI ablation	7.25 years/R

*On physical examination, **On radiology, ***Lenvatinib and larotrectinib.
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

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 B-Raf proto-oncogene (BRAF), telomerase reverse transcriptase (TERT), and rat sarcoma (RAS) genes are more frequent in adults compared to children, whereas neurotrophic tyrosine kinase receptors (NTRK) fusion oncogenes are seen at a high frequency in both children and adults (3,22). Additionally, RET/PTC rearrangements are 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 (23), while the impact of $BRAF^{V600E}$ mutation on the prognosis of childhood TC is not yet clear. 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 DICER1 syndrome (DICER1) (24,25). Genetic alternations were investigated in only two out of 10 previously reported cases (8,13). One was positive for RET/PTC rearrangement, who presented with extensive lymph node involvement that extended into the mediastinum. Nevertheless, there was no history of radiation exposure in this case, and he was in remission for a 1.5-year follow-up period (8). The other patient was positive for SQSTM1-NTRK3 fusion, which required targeted kinase inhibitors following surgery, and subsequently had RAI ablation (13). 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 when indicated. 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 (7). 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 (26). 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 performed in the immediate postoperative period. Observation with adequate TSH suppression was initially preferred. However, basal and stimulated Tg levels elevated in the first year following surgery, albeit with negative radiological progression, and 1 mCi/kg 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 (3). 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. Other than younger age, central and bilateral lymph node dissection, Graves' disease, thyroid cancer, total thyroidectomy, and reoperation are also predictors of postoperative hypoparathyroidism (27). Recent studies suggest that, along with assessing preoperative and postoperative calcium levels, measuring intraoperative PTH levels may be beneficial for anticipating the risk of postoperative hypocalcemia and the timing of parathyroid gland recovery (28). Although no postoperative complications were seen in our patient, as in the other reviewed patients, interestingly, he developed hypoparathyroidism in the third month after surgery. In the 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 (29). Secondary to RAI ablation, complications such as transient neck pain and edema, gastrointestinal symptoms, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eyes, nasolacrimal duct obstruction, secondary malignancies, and pulmonary fibrosis may develop. However, RAI is accepted to be safe in children since the side effects are dose-dependent (3,5). Furthermore, molecular targeted therapy has been demonstrated to be beneficial in children with PTC who have an advanced or refractory disease that is not amenable to RAI or further surgery (30). Mahajan et al (13) started targeted therapy (lenvatinib, subsequently switched to larotrectinib) for a five-year-old patient with NTRK3 fusion-positive metastatic PTC. They observed clinical stabilization and no side effects during five months of therapy. Patients with PTC require a regular follow-up by testing serum Tg level and performing neck ultrasonography. Target level of suppressed TSH should be obtained. In addition, if the Tg level increases and thyroid ultrasound is normal, a chest CT scan or a WBS should be performed. Our patient was followed up by a multidisciplinary team consisting of pediatric endocrinologists, surgeons, pathologists, radiologists, and 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. This is in contrast to previously published cases, in which follow-up strategy and long-term outcome results were not reported.

Conclusion

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 have been reported, and in most of these earlier cases long-term outcome was unavailable. The presented patient has had more than seven years disease-free. We suggest that this management strategy may be a road map for clinicians dealing with this rare cancer in very young children.

Ethics

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

Peer-review: Externally peer-reviewed.

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, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler, Literature Search: Ayşe Pınar Öztürk, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler, Writing: Ayşe Pınar Öztürk, Şükran Poyrazoğlu, Firdevs Baş, Feyza Darendeliler.

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