

# JCEM

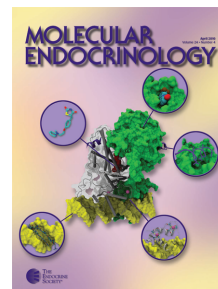
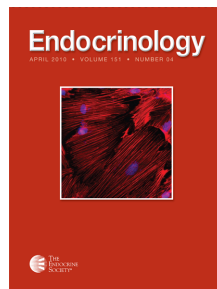
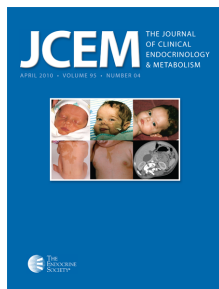
THE JOURNAL  
OF CLINICAL  
ENDOCRINOLOGY  
& METABOLISM

## Thyroid Nodules and Cancer in Children with PTEN Hamartoma Tumor Syndrome

Jessica R. Smith, Ellen Marqusee, Susan Webb, Vania Nose, Steven J. Fishman, Robert C. Shamberger, Mary C. Frates and Stephen A. Huang

J. Clin. Endocrinol. Metab. 2011 96:34-37 originally published online Oct 20, 2010; , doi: 10.1210/jc.2010-1315

To subscribe to *Journal of Clinical Endocrinology & Metabolism* or any of the other journals published by The Endocrine Society please go to: <http://jcem.endojournals.org/subscriptions/>



## Thyroid Nodules and Cancer in Children with PTEN Hamartoma Tumor Syndrome

Jessica R. Smith, Ellen Marqusee, Susan Webb, Vania Nose, Steven J. Fishman, Robert C. Shamberger, Mary C. Frates, and Stephen A. Huang

Thyroid Program of the Division of Endocrinology (J.R.S., S.W., S.A.H.), Department of Surgery (S.J.F., R.C.S.), and Vascular Anomalies Center (S.J.F.), Children's Hospital Boston, Boston, Massachusetts 02115; Thyroid Section of Division of Endocrinology, Diabetes, and Hypertension (J.R.S., E.M., S.A.H.), and Department of Radiology (M.C.F.), Brigham and Women's Hospital, Boston, Massachusetts 02115; and Department of Pathology (V.N.), University of Miami Miller School of Medicine, Miami, Florida 33136

**Context:** Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) is a complex disorder caused by germline-inactivating mutations of the PTEN tumor suppressor gene. Carriers develop benign and malignant tumors of multiple tissues, including the breast, thyroid, intestine, and skin. Surveillance to facilitate the early detection and treatment of malignancies is recommended but, because thyroid cancers have been reported almost exclusively in adults, childhood risk is considered to be low, and consensus guidelines recommend that surveillance imaging begin at 18 yr of age.

**Objective/Patients:** Seven children with PHTS referred to two thyroidologists form the basis of this report. Medical records, operative histology, and PTEN mutational analysis were reviewed to evaluate the pediatric presentation of PHTS-associated thyroid neoplasia.

**Results:** Five of the seven children presented with thyroid nodules or thyroid cancer between the ages of 6 and 12 yr, often as the initially identified component of their PHTS. Two others were diagnosed with PHTS on the basis of extrathyroidal features but had markedly abnormal screening ultrasounds with solid thyroid nodule(s) of at least 2 cm, despite the documentation of normal physical examinations. Five of the seven children in this cohort developed thyroid cancer.

**Conclusions:** Patients with PHTS can develop thyroid nodules and thyroid cancer in early childhood. This argues both for a high index of suspicion for PHTS in children diagnosed with multiple thyroid nodules and for careful thyroid surveillance in children diagnosed with PHTS. Because early detection improves the outcome of thyroid cancer, we recommend ultrasound surveillance for all patients upon the confirmation of a germline PTEN mutation, regardless of their age. (*J Clin Endocrinol Metab* 96: 34–37, 2011)

Germline mutations of the phosphatase and tensin homolog (PTEN) gene cause 85% of Cowden syndrome (MIM 158350; characterized by breast and thyroid cancers), 65% of Bannayan-Riley-Ruvalcaba syndrome (MIM 153480; characterized by macrocephaly, lipomatosis, hemangiomas, and speckled penis), and 20% of *Proteus* syndrome (MIM 176920; characterized by hamartomatous overgrowth, naevi, and hyperostoses) (1, 2).

This has led to the reclassification of these overlapping autosomal dominant disorders into the PTEN hamartoma tumor syndrome (PHTS) (2). The clinical management of PHTS focuses on cancer risk. Cowden syndrome is associated with a 25–50% lifetime risk of breast cancer, a 10% risk of thyroid cancer, and a 5–10% risk of endometrial cancer (2). The cancer risk of the Bannayan-Riley-Ruvalcaba and *Proteus* phenotypes is undefined but, because a

major component of these disorders is allelic to Cowden syndrome, cancer surveillance to facilitate early detection and treatment is recommended for all individuals with germline PTEN mutations (2).

Current consensus guidelines (3) recommend that thyroid surveillance consist of annual physical examinations, starting at age 18 yr or 5 yr younger than the youngest age of diagnosis of a component cancer in the family (whichever is younger). A baseline thyroid ultrasound is recommended at age 18 yr and can be considered annually thereafter (3). These guidelines reflect that PHTS-associated thyroid cancers have been reported almost exclusively in adults. However, here we report the presentation of not only thyroid nodules but also thyroid cancers in several young children with PHTS.

## Case Reports

All patients were euthyroid at presentation and have heterozygous PTEN mutations (Table 1). Patients 5 and 6 were included in a prior study of thyroid C-cell distribution (4). Patients 1, 6, and 7 were reported in a prior study of vascular anomalies in PHTS (5).

### Patient 1

This 12-yr-old boy presented with thyromegaly discovered on his pediatrician's physical exam. Sonography showed a multinodular goiter with a dominant left-sided nodule. The presence of lip and tongue papules led to the consideration of multiple endocrine neoplasia type 2B, but RET protooncogene testing was negative. Thyroidectomy revealed a left-sided, minimally invasive follicular carcinoma (4.5 cm) and multiple adenomatous nodules. The

patient was then referred to our center for evaluation and, because we noted penile freckling, PTEN testing was performed.

### Patient 2

This 6-yr-old girl presented with a neck mass noted by her older brother. Sonography showed a 2.9-cm right-sided nodule. Right thyroid lobectomy revealed a benign adenomatous nodule. Upon referral to our center, we noted macrocephaly. Her father had multiple lipomas, and palpation of his thyroid revealed a multinodular goiter. Based upon these features, we performed PTEN testing, which was positive in both the patient and her father. Of note, a 7-mm left-sided thyroid nodule was noted before right lobectomy. Repeat sonography 12 months later documented its growth to 1.6 cm (biopsied with benign cytology).

### Patient 3

This 10-yr-old girl presented with a neck mass noted by her mother. Sonography showed a 2-cm left-sided nodule. Subtotal thyroidectomy revealed a benign follicular adenoma. A second left-sided neck surgery was performed at 17 yr of age for "recurrent multinodular goiter," reporting benign nodular hyperplasia. During adolescence, the patient developed intestinal polyps and papular lesions of the extremities. A PTEN mutation was documented at 22 yr of age, and she was then referred to our center for thyroid surveillance. Her initial ultrasound discovered a 5.2-cm left neck mass that was shown to be papillary thyroid carcinoma upon resection. She received 150 mCi I-131, and an unstimulated serum thyroglobulin measurement 10 months later was undetectable.

**TABLE 1.** Clinical characteristics of patients with PHTS and associated thyroid neoplasia

Patient no.	Age at first thyroid surgery (yr)	Clinically significant thyroid pathology	Age at PTEN mutation diagnosis (yr)	PTEN mutation	Predicted effect
1	12	Follicular carcinoma	12	c.968dupA (exon 8)	Frame shift leading to premature termination one residue downstream.
2	6	Follicular adenomas	6	IVS8-1G>A (intron 8)	Destroy conserved splice donor site.
3	10	Follicular adenoma (1st surgery); benign nodules (2nd surgery); papillary carcinoma (3rd surgery)	22	c.609_611delTCCinsATAAAT (exon 6)	Premature termination at amino acid position 204.
4	7	Follicular carcinoma (1st surgery); papillary carcinoma (2nd surgery)	25	c.491delA (exon 5)	Frame shift leading to premature termination 2 residues downstream.
5	20	Follicular adenomas	20	c.389G>A (exon 5)	Normal arginine at amino acid position 130 replaced by glutamine (missense mutation).
6	11	Follicular adenomas with solitary papillary microcarcinoma	9	c.512–513insA (exon 6)	Frame shift leading to premature termination 8 residues downstream.
7	12	Follicular carcinoma	12	c.604_610delACTATTC (exon 6)	Frame shift leading to premature termination 17 residues downstream.

#### Patient 4

This 7-yr-old boy presented with a left-sided thyroid nodule discovered during a preoperative evaluation for tonsillectomy. Left thyroid lobectomy revealed a 2.8-cm follicular thyroid cancer with vascular invasion. Completion thyroidectomy and radioiodine therapy were declined. Throughout childhood, physical examinations of the neck were documented as normal. At 20 yr of age, he transferred care to our center, and neck sonography revealed multiple nodules in the right thyroid lobe (largest, 1.7 cm). Completion thyroidectomy showed multifocal papillary carcinoma. He received 60 mCi I-131, and an unstimulated serum thyroglobulin measurement 1 yr later was undetectable. Because his pediatric history was notable for renal cell carcinoma (a minor Cowden syndrome feature) and because he developed palmar pits and a scalp lipoma in adulthood, PTEN testing was performed at 25 yr of age.

#### Patient 5

This 8-yr-old boy presented with chronic diarrhea. Colonic biopsies showed inflammatory polyps and mucosal neuromas. Similar to patient 1, lip papules were present. Although RET protooncogene testing was negative, he was monitored through childhood with annual thyroid palpation and pentagastrin-stimulation tests. At 20 yr of age, PTEN testing was performed secondary to penile freckling. Although thyroid palpation was reportedly normal, he was then referred to our center for thyroid surveillance. His initial thyroid sonogram revealed four nodules larger than 2.5 cm and over 10 additional nodules larger than 1 cm. Thyroidectomy showed benign adenomatous nodules.

#### Patient 6

This 9-yr-old girl presented to genetics clinic because her maternal uncle was diagnosed with Cowden syndrome. Her medical history was notable for macrocephaly and intestinal polyps. Genetic testing confirmed a PTEN mutation, and, in accordance with consensus guidelines (3), thyroid palpation was performed annually. At 11 yr of age, a thyroid ultrasound obtained to address discordant physical examinations (one physician documented a normal thyroid, whereas a second appreciated left-sided enlargement) showed a 2.0-cm nodule in the left thyroid lobe. Thyroidectomy revealed multiple follicular adenomas with a papillary microcarcinoma in the largest adenoma.

#### Patient 7

This 12-yr-old boy underwent genetic testing secondary to penile freckling and a characteristic lower extremity

arteriovenous malformation (5). Upon confirmation of a PTEN mutation, a baseline sonogram was performed, revealing a 2.3-cm right-sided thyroid nodule. He was referred to our center where biopsy showed suspicious cytology. Right thyroid lobectomy revealed a follicular carcinoma with vascular invasion, prompting completion thyroidectomy and ablation with 60 mCi I-131. Serum thyroglobulin measurements have been undetectable for 3 yr postoperatively.

### Methods

Seven patients referred to two thyroidologists form the basis of this report. Patient inclusion required surgical thyroidectomy and a documented PTEN mutation. Studies were approved by our institutions' Investigative Review Boards. PTEN testing was performed in the Molecular Pathology Laboratory of Ohio State University (Columbus, OH) for patient 5; in the research laboratory of Dr. Charis Eng at Ohio State University for patient 6; and in GeneDx (Gaithersburg, MD) for all others (6).

### Results and Discussion

This study reveals an association between the rare entities of PHTS and childhood thyroid cancer. In this series of seven children, four patients (patients 1–4) presented with thyroid nodules between the ages of 6 and 12 yr as the initially identified component of their PHTS. Two others (patients 5 and 6) were diagnosed with PHTS on the basis of extrathyroidal features but had markedly abnormal screening ultrasounds, despite the documentation of normal thyroid palpation 8 months or 2 months before imaging. The final patient in this series (patient 7) was referred directly to thyroid sonography upon the diagnosis of PHTS, leading to the discovery of a follicular carcinoma at 12 yr of age. Five of the seven children in this cohort (patients 1, 3, 4, 6, and 7) developed thyroid cancer. Interestingly, although only Cowden syndrome has previously been associated with thyroid cancer risk, several patients had penile freckling or other clinical features of Bannayan-Riley-Ruvalcaba syndrome (2).

Before the patients in this current series, PHTS-associated follicular cell-derived thyroid cancers were reported exclusively in individuals with Cowden syndrome and, to our knowledge, in only one other child (5, 7). This is the basis of the current recommendation to defer surveillance thyroid sonography to adulthood (3), but the current study illustrates how the lack of pediatric reports may be explained by diagnostic limitations before the recent availability of PTEN testing. Before mutational testing, Cowden syndrome was diagnosed by pathognomonic mucocutaneous lesions that manifest in late adolescence, so

occult thyroid cancers were discovered only after surveillance was initiated in adulthood. Conversely, rare individuals (such as patients 1 and 4) diagnosed with thyroid cancer in childhood would fail to meet clinical diagnostic criteria for Cowden syndrome upon presentation, and so the association between their thyroid disease and PHTS would again go unrecognized.

Because patient numbers were small and PTEN testing was only performed in children with suspicious features, the precise frequency of PTEN mutations cannot be accurately estimated by this retrospective study. However, this case series suggests that a significant minority of children referred for thyroid nodules may have germline PTEN mutations, and we recommend a careful history to evaluate for signs of PHTS. If characteristic PHTS features (reviewed in Ref. 2) are present in the patient or in older relatives, genetic testing should be performed. The diagnosis of a germline PTEN mutation permits the identification of affected relatives and the early treatment of other PHTS-associated malignancies such as breast cancer. Notably, although PTEN testing was not performed, one retrospective study of 112 children with thyroid cancer reported two patient deaths from “rapidly progressive breast cancer” 13 or 15 yr after thyroid cancer diagnosis (8).

We acknowledge that lack of follow-up on patients who transferred care to local physicians limits our ability to assess long-term outcome. Furthermore, because this report is limited to a single tertiary center, ascertainment and referral bias are potential confounders. Although we do not know the thyroid cancer risk of children with PHTS from this small case series, our data suggest that vigilance is warranted. Widely available commercial PTEN testing now permits the routine identification of childhood carriers, and early detection is known to improve thyroid cancer outcome. Thyroid sonography is more accurate than palpation (9, 10) and may be especially helpful in pediatrics where, due to the much lower frequency of thyroid nodules, clinicians may be inexperienced in their palpation. We recommend that a baseline thyroid ultrasound be performed in all patients upon the diagnosis of PHTS, regardless of their age, and then repeated annually. If a thyroid nodule of at least 1 cm is detected in a child with a normal TSH, it should be evaluated with ultrasound-guided fine-needle aspiration, and standard guidelines for thyroid surgery should be applied (10). Because PHTS is the result of germline mutation and even optimal thyroid surgery routinely leaves a thyroid remnant, continued surveillance is warranted after the resection of benign nodules for the risk of disease progression as was observed in patient 3. In such individuals, we suggest that postoperative

levothyroxine replacement be titrated to a low normal serum TSH and that serum thyroglobulin be measured annually. If serum thyroglobulin becomes detectable or antithyroglobulin antibodies confound its measurement, annual sonography should be added.

## Acknowledgments

We thank Dr. P. Reed Larsen for helpful insights and comments on this manuscript.

Address all correspondence and requests for reprints to: Stephen A. Huang, Children’s Hospital Boston, 300 Longwood Avenue, Boston, Massachusetts 02115. E-mail: stephen.huang@childrens.harvard.edu.

Disclosure Summary: The authors have nothing to disclose.

## References

1. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R 1997 Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 16:64–67
2. Pilarski R, Eng C 2004 Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. *J Med Genet* 41:323–326
3. Daly MB, Axilbund JE, Buys S, Crawford B, Farrell CD, Friedman S, Garber JE, Goorha S, Gruber SB, Hampel H, Kakkamani V, Kohlmann W, Kurian A, Litton J, Marcom PK, Nussbaum R, Offit K, Pal T, Pasche B, Pilarski R, Reiser G, Shannon KM, Smith JR, Swisher E, Weitzel JN 2010 Genetic/familial high-risk assessment: breast and ovarian. *J Natl Compr Canc Netw* 8:562–594
4. Zambrano E, Holm I, Glickman J, Huang S, Perez-Atayde A, Kozakewich HP, Shamberger RC, Nosé V 2004 Abnormal distribution and hyperplasia of thyroid C-cells in PTEN-associated tumor syndromes. *Endocr Pathol* 15:55–64
5. Tan WH, Baris HN, Burrows PE, Robson CD, Alomari AI, Mulliken JB, Fishman SJ, Irons MB 2007 The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. *J Med Genet* 44:594–602
6. den Dunnen JT, Antonarakis SE 2000 Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. *Hum Mutat* 15:7–12
7. Lachlan KL, Lucassen AM, Bunyan D, Temple IK 2007 Cowden syndrome and Bannayan Riley Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of PTEN mutation carriers. *J Med Genet* 44:579–585
8. Vassilopoulou-Sellin R, Goepfert H, Raney B, Schultz PN 1998 Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up. *Head Neck* 20:549–555
9. Marqusee E, Benson CB, Frates MC, Doubilet PM, Larsen PR, Cibas ES, Mandel SJ 2000 Usefulness of ultrasonography in the management of nodular thyroid disease. *Ann Intern Med* 133:696–700
10. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19:1167–1214