

Appendix A: Patients with PHTS who present with thyroid benign nodular disease or differentiated thyroid carcinoma before the age of 18

Case nr.	Sex	Diagnosis PHTS	PTEN mutation	Age at diagnosis first thyroid disease (years)	(Benign) nodular disease	Age first thyroid cancer	(Differentiated) thyroid carcinoma	Treatment	Reference
1	M	CS	Yes	8	Adenomatous nodules			Lymph node removal	This manuscript
2	F	CS	Yes	4	Graves' disease Lymphocytic thyroiditis	9	Metastasized papillary thyroid carcinoma	Total thyroidectomy	This manuscript
3	F	CS	No	13	- Follicular adenomas - Adenomatous nodules - Colloid nodule			Total thyroidectomy	Harach et al. (1)
4	M	CS	No	9	- Follicular adenoma - Colloid cyst	27	Follicular neoplasm	Subtotal thyroidectomy	Harach et al. (1)
5	M	PHTS	Yes	12	Multiple adenomatous nodules	12	Minimal invasive follicular carcinoma (4,5 cm)	Thyroidectomy	Smith et al. (2)
6	F	PHTS	Yes	6	Multiple follicular adenomas			Subtotal thyroidectomy	Smith et al. (2)
7	F	PHTS	Yes	10	Follicular adenoma	22	Papillary thyroid carcinoma	Subtotal thyroidectomy	Smith et al. (2)

8	M	PHTS	Yes			7	Follicular thyroid cancer with vascular invasion	Subtotal thyroidectomy	Smith et al. (2)
9	F	PHTS	Yes	11	Multiple follicular adenomas	11	Papillary microcarcinoma	Total thyroidectomy	Smith et al. (2)
10	M	PHTS	Yes			12	Follicular carcinoma with vascular invasion	Total thyroidectomy and ablation	Smith et al. (2)
11	M	BRRS	Yes	12	- Multiple adenomatous nodules - Lymphocytic thyroiditis - Diffuse C-cell hyperplasia	12	Follicular carcinoma		Laury et al. (3)
12	M	BRRS	Yes	7	Lymphocytic thyroiditis	7	Minimally invasive follicular carcinoma		Laury et al. (3)
13	F	BRRS	Yes	11	- Follicular adenomas - Focal C-cell hyperplasia	11	Papillary thyroid micro carcinoma		Laury et al. (3)
14	M	BRRS	Yes	13	- Lymphocytic thyroiditis - Focal C-cell hyperplasia	13	Follicular carcinoma, minimally invasive		Laury et al. (3)
15	F	BRRS	Positive	13	- Multiple adenomatous nodules - Follicular adenoma				Laury et al. (3)
16	?	CS	Not tested			6	Multifocal thyroid carcinoma	Thyroidectomy	Hachicha et al. (4)

17	M	CS	Yes	12	Multiple adenomatous nodules				Mcheik et al. (5)
18	F	PHTS	Yes			17	Thyroid cancer		Ngeow et al. (6)
19	M	PHTS	Yes			7	Thyroid cancer		Ngeow et al. (6)
20	M	BRRS	Yes	10	Nodules	14	Hurthle-cell (oxyphillic) carcinoma	Total thyroidectomy	Peiretti et al. (7)
21	F	BRRS	Yes	8	Follicular adenoma			Total thyroidectomy	Peiretti et al. (7)
22	F	BRRS	Yes	9	Hürthle cell adenoma			Total thyroidectomy	Stein et al. (8)
23	M	BRRS	Not tested	9	Follicular adenoma			Subtotal thyroidectomy	Ekinci et al. (9)
24	M	BRRS	Not tested	14	Diffuse goiter				Ekinci et al. (9)
25	M	BRRS	Not tested	11	Multinodular goiter				Erkek et al. (10)
26	M	BRRS	Yes	9	Goiter				Hendriks et al. (11)
27	F	CS	Not tested	16	Nodules			Partial Thyroidectomy	Alexander et al. (12)

28	F	CS	Yes	11	- Multiple follicular adenomas - Adenomatous nodules - C-cell hyperplasia	11	Papillary microcarcinoma		Zombrano et al. (13)
29	M	CS	Yes			15	Thyroid cancer	Total thyroidectomy	Oliveira et al. (14)
30	M	CS	Not tested			17	Medullary carcinoma	Total thyroidectomy	Koksal et al. (15)
31	M	CS	Yes	8	Follicular adenoma			Subtotal thyroidectomy	Devi et al. (16)
32	F	CS	Not tested	13	Multinodular adenomatous goiter			Partial thyroidectomy	Wells et al. (17)
33	M	CS	Not tested	13	Nodule				Nuss et al. (18)
34	F	CS	Not tested	12	- Goiter - Cold nodules				Aram& Zidenbaum (19)
35	M	PHTS	Yes			14	Thyroid carcinoma (non-medullary)		Tan et al. (20)
36	F	PHTS	Yes			15	Thyroid carcinoma (non-medullary)		Tan et al. (20)
37	F	PHTS	Yes	13	-Thyroid adenoma - Multiple nodules	14	Thyroid carcinoma (non-medullary)		Tan et al. (20)
38	M	PHTS	Yes	13	- Thyroid adenoma - Multiple nodules				Tan et al. (20)

39	M	PHTS	Yes			15	Follicular thyroid carcinoma		Lachlan et al. (21)
40	F	CS	Not tested	13	Multinodular adenomatous goiter			Total thyroidectomy	Laugier et al. (22)
41	M	BRRS	Yes			4	Follicular thyroid carcinoma, minimally invasive		Nyzuki et al. (23)
42	F	PHTS	Yes	6	Nodular goiter			Total thyroidectomy	Plamper et al. (24)
43	M	PHTS	Yes	9	Follicular adenoma			Total thyroidectomy	Plamper et al. (24)
44	M	PHTS	Yes	5	Follicular adenoma	6	Papillary microcarcinoma	Total thyroidectomy	Plamper et al. (24)
45	F	PHTS	Yes	6	Follicular nodule			Total thyroidectomy	Plamper et al. (24)
46	M	PHTS	Yes	7	Nodular goiter			Total thyroidectomy	Plamper et al. (24)
47	M	PHTS	Yes	11	Follicular adenoma (2x)			Total thyroidectomy	Plamper et al. (24)
48	F	PHTS	Yes	13	Follicular microadenoma	13	Follicular carcinoma	Total thyroidectomy and radioiodine therapy	Plamper et al. (24)
49	M	CS	Yes	17	- Adenomatous nodule - Graves' disease Lymphocytic thyroiditis			Total thyroidectomy	Patraquim et al. (25)
50	F	PHTS	Yes	15		15	Thyroid cancer	Total thyroidectomy and radioactive iodine therapie	ElNaggar et al. (26)
51	F	CS	Yes	17		17	Follicular thyroid carcinoma	Hemithyroidectomy	Bouron-Dal Soglio et al. (27)
52	F	CS	Yes	14	Follicular adenomas				Girardin et al. (28)

53	M	BRRS	Yes			7	Metastasized follicular thyroid carcinoma		Hay et al. (29)
54	M	PHTS	Yes	15	Follicular adenomas	15	Follicular thyroid carcinoma	Total thyroidectomy	Esen & Okdemir (30)
55	F	CS	No			11	Follicular thyroid carcinoma	Hemithyroidectomy	Joshi et al. (31)
56	F	PHTS	Yes	13	Thyroid nodules				Nakagawa et al. (32)
57	F	PHTS	Yes	14	- Multinodular goiter - Lymphocytic thyroiditis				Tosur et al. (33)

Abbreviations: CS, Cowden syndrome; PHTS, PTEN Hamartoma Tumor Syndrome; BRRS, Bannayan Riley Ruvalcaba syndrome

Appendix B: Mode of discovery, screening strategy, and disease outcome of pediatric patients with PHTS diagnosed with thyroid benign nodular disease or differentiated thyroid carcinoma

Case number	Mode of discovery	Screening strategy	FNA results	Disease Outcome	Reference
1	Routine thyroid ultrasound	Annual thyroid ultrasound	FNA suspect lymph node, no malignancy	Follow up time 5 years: no abnormalities	This manuscript
2	Upon histology	Annual thyroid ultrasound		At age 15 years: no suspicious lesions	This manuscript
5	Goiter on physical exam, subsequent ultrasonography				Smith et al. (2)
6	Neck mass noted by older brother, subsequent ultrasonography	Follow-up 12 months to monitor growth of nodules		At follow-up ultrasound 12 months post diagnosis growth of 1 nodule was reported	Smith et al. (2)
7	At age 10 years: neck mass noted by mother, subsequent ultrasonography At age 22 years: surveillance ultrasound	Unknown until the age of 22 years, From then on: ultrasound of unknown frequency		After I-131 treatment: 10 months later serum thyroglobulin undetectable At age 17 years: recurrent MNG	Smith et al. (2)
8	Thyroid lesion discovered during preoperative evaluation for tonsillectomy	Physical examination of neck From age 20 years: ultrasound		At age 20 years: multifocal papillary carcinoma	Smith et al. (2)
9	Thyroid lesion discovered by ultrasound after discordant physical examination of two clinicians	Annual palpation of thyroid from diagnosis onwards			Smith et al. (2)
10	Thyroid lesion discovered after baseline ultrasound	Baseline US after diagnoses PHTS		3 years postoperatively: undetectable serum thyroglobulin	Smith et al. (2)
12				At age 20 years: multifocal PTC	Laury et al. (3)

16	After observation of a neck mass thyroid lesion was confirmed by ultrasound			Follow up at age 18 years: no abnormalities reported	Hachicha et al. (4)
18				At adult age: secondary endometrial and ovarian cancers	Ngeow et al. (6)
19				At age 21 years: secondary renal cancer	Ngeow et al. (6)
20	Age 10 years: clinical evaluation enlarged thyroid was noted Age 14 years: routine ultrasound screening noted growth of nodule	From age 10 years: tri-annual thyroid ultrasound	Age 14 years: FNAC revealed Hürthle-cell carcinoma	At follow up until age 22 years: no additional thyroid disease reported	Peiretti et al. (7)
21	Two constitutive thyroid US revealed growing nodule	Bi-annual thyroid ultrasound from diagnosis PHTS and anti-thyroglobulin antibody blood test	Age 8 years: FNA showed 'suspect' cytology	Iatrogenic hypothyroidism with levothyroxine replacement	Peiretti et al. (7)
22	Baseline ultrasound revealed thyroid lesion				Stein et al. (8)
23	Palpation during physical examination revealed a nodule				Ekinci et al. (9)
24	Ultrasound showed thyroid lesions, subsequent scintigraphy showed diffuse hyper-plasticity	Conservative follow up of thyroid nodules			Ekinci et al. (9)
25	Baseline ultrasound revealed thyroid pathology				Erkek et al. (10)
26	Palpation at physical examination				Hendriks et al. (11)

27			At age 30 years: hypoparathyroidism and nodule At age 34 years: nodule with calcifications	Alexander et al. (12)
30	Palpation at physical examination	Malignant thyroid cells		Koksal et al. (15)
31			At age 12 years: multinodular goiter, followed by total thyroidectomy	Devi et al. (16)
34	Palpation at physical examination			Aram& Zidenbaum (19)
42	Baseline ultrasound			Plamper et al. (24)
43	Ultrasound screening			Plamper et al. (24)
44	Ultrasound screening			Plamper et al. (24)
45	Ultrasound screening			Plamper et al. (24)
46	Ultrasound screening			Plamper et al. (24)
47	Ultrasound screening			Plamper et al. (24)
48	Palpable neck mass and subsequent ultrasound			Plamper et al. (24)
49	Ultrasound screening	Benign		Patraquim et al. (25)
50	Ultrasound screening		Three year remission	ElNaggar et al. (26)
51	Palpable neck mass and subsequent ultrasound	Follicular neoplasm	At 7 years follow-up: recurrent metastasized FTC	Bouron-Dal Soglio et al. (27)
52	Ultrasound screening			Girardin et al. (28)
53	Palpable neck mass and	Non-diagnostic	‘several’ years follow up: no	Hay et al. (29)

	subsequent ultrasound	abnormalities	
54	Neck mass noted by mother	Suspicious for follicular neoplasm	Esen & Okdemir (30)
55	Palpable neck mass and subsequent ultrasound	Features consistent with a follicular neoplasm were identified	Joshi et al. (31)

Abbreviations: PHTS, PTEN Hamartoma Tumor Syndrome; MNG, multi nodular goiter; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma

References Appendix A and B

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