Papillary thyroid carcinoma in a boy with familial tuberous sclerosis complex attributable to a TSC2 deletion—a case report

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ABSTRACT

Tuberous sclerosis complex (TSC), a phacomatosis, is a rare genetic disease (autosomal dominant; incidence: 1 in 6,800–17,300) associated with mutations in the TSC1 and TSC2 genes, 70% of which are sporadic. The disease causes benign tumours in the brain, kidneys, heart, lungs, skin, and eyes; thyroid lesions are extremely rare.

A 13-year-old euthyroid boy with a hereditary form of TSC (del 4730G in TSC2, also seen in 2 sisters and the father) was admitted to hospital with a thyroid nodule. Physical examination revealed a nodular left lobe with increased consistency. Thyroid ultrasonography revealed a heterogeneous left lobe, predominantly hypoechoic with multiple microcalcifications and the presence of suspicious cervical lymph nodes on the left side. A macrocalcification was observed on the right lobe. Fine-needle biopsy results showed a few groups of cells with discrete characteristics, including abundant cytoplasm, nuclei with conspicuous nucleoli, intra-nuclear inclusions, and nuclear grooves. The patient underwent total thyroidectomy with lymphadenectomy. Histopathology examination confirmed papillary thyroid carcinoma.

The coincidence of endocrine neoplasia including thyroid cancer and TSC is rare, and TSC with papillary thyroid carcinoma has never been described in a child. Studies of mutations in the tumour suppressor genes TSC1, TSC2, and STK11, activating the mTOR (mammalian target of rapamycin) pathway, might support their role in the pathogenesis of thyroid cancer.

Key Words Children, thyroid cancer, tuberous sclerosis

INTRODUCTION

Thyroid carcinoma accounts for 1%–1.5% of malignancies in children. Sporadic differentiated cancers constitute most of those malignancies, and papillary thyroid carcinoma (PTC) constitutes 60%–80% of the latter type1.

The clinical manifestation of PTC is different in children and adults. In children, PTC is usually diagnosed at a more advanced stage, resulting in a greater frequency of lymph node and distant metastases at the time of diagnosis. Despite those features, prognosis is better in children than in adults. Researchers postulate that thyroid carcinomas in the pediatric population present a higher grade of differentiation and a better response to adjuvant treatment (radioactive iodine followed by suppressive therapy with l-thyroxine). Theories proposed to explain this phenomenon focus on the low incidence of BRAF mutations in children. The BRAF mutations—in particular, BRAF V600E—result in dysfunction of the sodium iodide symporter protein and thus resistance to radioiodine therapy2–4. The sex distribution of thyroid carcinomas varies with age, having a female:male ratio of 4:1 in adults and 1.5:1 in children under the age of 15 years. Thyroid ultrasonography and fine-needle aspiration biopsy are key preoperative diagnostic tools in thyroid nodule examination4.

Tuberous sclerosis complex (TSC), which belongs to a group of neurocutaneous diseases termed phacomatoses, is a rare genetic disorder caused by mutations in either of two tumour suppressor genes: TSC1, located on chromosome 9q34, or TSC2, located on chromosome 16p13.3.
Approximately 70% of tsc cases represent sporadic gene mutations; in other patients, tsc is inherited in an autosomal-dominant pattern. However, in 10%–15% of patients, no mutation is identified by conventional genetic testing. The estimated prevalence of tsc, 1:6000, is similar in female and male patients.

Tuberous sclerosis complex is characterized by the formation of hamartomas in multiple organs, particularly the kidneys, heart, brain, lungs, skin, and eyes. Data concerning the occurrence of lesions within the thyroid gland are extremely scarce.

**CASE DESCRIPTION**

A 13-year-old boy known to have tsc (positive family history: the father and 2 younger sisters of the patient also have tsc; Figure 1) was admitted to the Department of Pediatric Endocrinology and Rheumatology of the Poznan University of Medical Sciences for a diagnostic workup of the thyroid. At the age of 6, he had been diagnosed with tsc because of the appearance of facial angiofibromas (Pringle nodules, Figure 2), hepatic and renal angiomyolipomas, a hamartoma of the left eye, depigmented skin patches, and magnetic resonance imaging findings of the head characteristic of tsc (subependymal nodules and cortical tubers).

The clinical diagnosis was further confirmed by genetic testing: a 4730G deletion within exon 36 of the TSC2 gene was identified in all affected family members.

Computed tomography (CT) imaging of chest and partial neck before admission revealed numerous nodules or lesions in the lungs, 4 mm and 2 mm in diameter respectively, and an enlarged multinodular left thyroid lobe with microcalcifications. The physical examination at admission revealed a palpable left thyroid lobe with increased consistency and a nodular character. The left thyroid lobe was completely nodular on ultrasonography, and multiple hypoechoic areas with numerous microcalcifications were visible (Figure 3(A–C)). Increased blood flow on power Doppler was also observed (Figure 3(C,D)). Additionally, 2 microcalcifications surrounded by a hypoechoic halo were visible in the right thyroid lobe, one between the upper and central part of the right lobe, and the other located peripherally. Suspicious lymph nodes with microcalcifications were also reported posterior to the left sternocleidomastoid muscle (Figure 3(E,F)).

The patient was euthyroid on both clinical and hormonal assessment. His calcium and phosphate parameters were also normal (Table 1). Thyroid scintigraphy with 99mTc [150 MBq (4 mCi)] showed a focal area of no tracer uptake in the upper pole of the left lobe (“cold area”). An ultrasound-guided fine-needle aspiration biopsy of the left thyroid lobe revealed clusters of cells with minor atypical features, including abundant cytoplasm, conspicuous nucleoli, intra-nuclear inclusions, and irregular nuclear membranes termed “nuclear grooves” (Figure 4).

The diagnosis of suspicious for thyroid cancer was subsequently made (category 5 based on the Bethesda system).

The patient qualified for total thyroidectomy with elective lymphadenectomy. The surgery was performed uneventfully, and postoperative histopathology findings confirmed the diagnosis of a multifocal, unencapsulated, clear-cell variant of ptc with central cervical lymph node metastases, multiple vascular thromboses, and infiltration of the thyroid capsule [pT1bmN1aM0 by the 2002 staging system of Union for International Cancer Control, Figure 5(A–C)]. The maximum diameter of a single cancerous focus did not exceed 1.2 cm.

By immunohistochemistry, the carcinoma cells were positive for these neoplastic markers: thyroid transcription factor 1 (nuclear reaction), beta-catenin (cytoplasmic

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**FIGURE 1** Patient’s family pedigree.

**FIGURE 2** Clinical presentation of the patient.
reaction), cytokeratin 19, cytokeratin AE1/AE3, thyroglobulin (focally), Ki-67, and vimentin. No expression of synaptophysin, chromogranin A, carciinoembryonic antigen, S100, or Bcl-2 was observed. Most of the tumour cells showed a negative reaction to Ki-67.

After surgery, l-thyroxine suppressive therapy (100 μg daily) was initiated according to the guidelines of the Polish Group for Endocrine Tumours\textsuperscript{10}. Several weeks later, the patient’s serum thyroid stimulating hormone (TSH) was 1.026 μIU/mL, and his serum free thyroxine was 1.01 ng/dL; the dose of l-thyroxine was therefore increased to 125 μg daily. His postoperative serum thyroglobulin was 2.95 ng/mL.

Six months after surgery, diagnostic scintigraphy of neck and total body showed iodine uptake exclusively in the neck [1.7%, Figure 6(A)]. Numerous suspicious lymph nodes were noted on both sides of the neck on ultrasonography examination, and serum thyroglobulin had increased to 15.38 ng/mL. The endogenous TSH surge was 156,396 μIU/mL, and additional therapy with 3700 MBq (100 mCi) \textsuperscript{131}I was given. In post-therapeutic scintigraphy, \textsuperscript{131}I uptake was present only in the thyroid bed (more intense on the left side). No pathologic foci were present in the whole-body scan. Suppressive therapy with l-thyroxine (targeted dose: 125 μg) was reintroduced.

Two months later, serum TSH was 0.1759 μIU/mL, and serum thyroglobulin was 1.78 ng/mL, with negativity for thyroglobulin autoantibodies. No radiologic features of PTC relapse were observed on CT imaging of neck and chest; however, an additional lesion in the lungs, 4 mm in diameter, was noticed.

**FIGURE 3** Thyroid ultrasonography images. (A,B) Nodular left thyroid lobe with multiple hypoechoic areas and numerous microcalcifications. (C,D) Increased blood flow is observed on power Doppler. (E,F) Metastatic lymph nodes with microcalcifications are shown posterior to the left sternocleidomastoid muscle.

**TABLE I** Biochemical parameters in the patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Reference range</th>
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<tr>
<td>Thyroid stimulating hormone (μIU/mL)</td>
<td>1.040</td>
<td>0.470–4.640</td>
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<td>Free thyroxine (ng/dL)</td>
<td>0.85</td>
<td>0.71–1.85</td>
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<tr>
<td>Free triiodothyronine (pg/mL)</td>
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<td>1.45–3.48</td>
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<td>Thyroid peroxidase antibody (IU/mL)</td>
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<td>&lt;5.61</td>
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<tr>
<td>Thyroglobulin antibody (IU/mL)</td>
<td>0.7</td>
<td>&lt;4.11</td>
</tr>
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<td>Parathyroid hormone (pg/mL)</td>
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<td>15–65</td>
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<td>Betal human chorionic gonadotropin (mIU/mL)</td>
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<td>&lt;5</td>
</tr>
<tr>
<td>Alpha fetoprotein (ng/mL)</td>
<td>1.76</td>
<td>&lt;7</td>
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<tr>
<td>Carciinoembryonic antigen (ng/mL)</td>
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<td>&lt;5</td>
</tr>
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<td>Calcium (mmol/L)</td>
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<tr>
<td>Phosphate (mg/dL)</td>
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</table>

**FIGURE 4** Fine-needle aspiration biopsy specimen. Clusters of cells show atypical features, including abundant cytoplasm, nuclei with conspicuous nucleoli, intra-nuclear inclusions, and nuclear grooves (category 5 by the Bethesda system). May–Grünewald Giemsa stain, 400× original magnification.
Six months later, serum TSH was 2.6424 μIU/mL, and serum thyroglobulin was 1.20 ng/mL. The L-thyroxine dose was slightly increased to 125 μg twice weekly, and 137 μg 5 times weekly.

Eight months after 131I treatment, the neck and total-body scans showed no 131I uptake [Figure 6(B)]; however, the endogenous TSH-induced thyroglobulin level had increased to 13.40 ng/mL. (Thyroglobulin autoantibodies were negative.) Based on the thyroglobulin level and ultrasonography examination (suspicious lymph nodes on the left side of the neck), a fine-needle aspiration biopsy was performed, followed by another surgery. The histopathology results confirmed a clear-cell variant of PTC in the 2 excised lymph nodes.

Four months later, the neck and total-body 131I scan did not show any uptake [Figure 6(C)], and serum thyroglobulin was 1.15 ng/mL (thyroglobulin autoantibodies were negative). A second dose of 131I was given, followed by L-thyroxine therapy (137 μg daily).

Currently, the patient is disease-free on L-thyroxine suppression therapy (137 μg daily; serum TSH: 0.43 μIU/mL).

**DISCUSSION AND CONCLUSIONS**

The coincidence of endocrine cancer and TSC is extremely rare. Only a few cases of endocrine tumours such as parathyroid adenoma11, pheochromocytoma, insulinoma12, or medullary thyroid carcinoma13 have been reported in TSC patients. To date, no case of TSC and PTC coexisting in a pediatric patient has been reported.

In healthy individuals, the protein products of the TSC1 and TSC2 genes, hamartin and tuberin respectively, generate a functional complex that inhibits the mTOR (mammalian target of the rapamycin) signalling pathway14. Mutations in the TSC1 and TSC2 genes result in overexpression of the mTOR pathway, resulting in the formation of neoplasms in various organs15. Based on experimental findings regarding the mechanism underlying TSC, mTOR inhibitors, including everolimus, were introduced for the therapy of TSC [the U.S. Food and Drug Administration first registered everolimus for the treatment of advanced renal cancer in 2009]. The efficacy and safety of mTOR inhibitors for the treatment of various neoplasms—for example, subependymal giant-cell astrocytoma, renal angiomyolipoma, or sporadic lymphangioleiomyomatosis—was demonstrated16–18. Moreover, single reports about the efficacy of everolimus therapy for cardiac rhabdomyoma can be found in the literature19. In 2014, Wagle et al.20 described a patient with an advanced anaplastic thyroid carcinoma in whom therapy with everolimus resulted in an 18-month remission.
Patients with tsc present with a wide range of neuro-psychiatric disorders, termed tuberous sclerosis complex-associated neuro-psychiatric disorders. De Vries and Howe examined the role of the hamartin–tuberin complex as the global regulator and integrator of a spectrum of physiologic processes and found that a disruption of the signaling pathway in the brain might be directly responsible for the neurocognitive features in tsc patients. The potential benefit of everolimus for the treatment of neuropsychiatric disorders was reported in a patient with tsc, in whom everolimus therapy was introduced because of the occurrence of subependymal giant-cell astrocytoma, leading to a remarkable improvement of selective mutism.

Here, we describe the first case of ptc in a young patient with tsc. The second-hit hypothesis of the germline tsc mutation and a somatic mutation of this suppressor gene cannot be excluded. Further investigations of mutations in suppressor genes are required, because they might offer new insights into the diagnostic and therapeutic processes of thyroid carcinomas.

In all cancers, an early diagnosis is of great significance for prognosis. Patients with tsc should therefore regularly undergo abdominal ultrasonography examination, magnetic resonance imaging of the head, and chest ct for assessment of lung disease. Given that some cases of thyroid carcinoma have been described in tsc, ultrasonography exams are recommended, given that ct is not the “gold standard” technique for thyroid evaluation.

The cause of the single-lung lesions on ct imaging that are reported here (4 mm or less in diameter) remains unknown. The most likely possibility is a tsc-related process (multifocal micro-nodular pneumocyte hyperplasia), but other infectious or post-infectious causes (tuberculosis, fungal or viral pneumonitis, nodcariosis, salmonellosis) and non-infectious causes [miliary metastases (thyroid carcinoma, renal-cell carcinoma, breast carcinoma, malignant melanoma, pancreatic neoplasms, osteosarcoma, and trophoblastic disease], sarcoidosis, pneumoconiosis, pulmonary hemosiderosis, bcg-osis, hypersensitivity pneumonitis, pulmonary alveolar proteinosis] should be considered in the differential diagnosis. However, those alternative conditions usually manifest as miliary pulmonary opacities and not all of them occur in this age group.

Moreover, in this particular patient with clear-cell ptc and tsc, serum thyroglobulin was a much more sensitive and potent marker of residual thyroid cancer than 131i scintigraphy. Thus, ultrasonography of the neck is recommended for the screening of patients with genetically proven tsc and for follow-up of patients with ptc even if 131i scintigraphy is negative. Initial treatment with mtor inhibitors was postponed because of the patient’s oncologic status and lesions of the chest on ct imaging; however, based on the patient’s current oncologic status (disease-free based on both scintigraphy and serum thyroglobulin), treatment with everolimus was initiated.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none related to the present manuscript.

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