A Case Report of Syndromic Multinodular Goitre in Adolescence: Exploring the Phenotype Overlap between Cowden and DICER1 Syndromes

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What Is Known about This Topic?

- Clinicians should be suspicious of an underlying genetic aetiology when a child or adolescent presents with nodular thyroid disease and a history of familial malignancy or syndrome-related diseases. Targeted testing for a genetic predisposition syndrome is based on the phenotypic presentation of the patient and relatives.

What Does This Case Report Add?

- We present a case report of an adolescent female who developed multiple tumours, the spectrum of which could be attributed to either Cowden or DICER1 syndromes. A *PTEN* mutation was discovered, highlighting rare manifestations of Cowden syndrome including ovarian germ cell tumour and lung cysts.

Keywords

Thyroid nodules · *PTEN* · DICER1 syndrome · Mutations · Cowden syndrome · Hereditary

Abstract

Background: Hereditary tumour predisposition syndromes may increase the risk for development of thyroid nodules at a young age. We present the case of an adolescent female with Cowden syndrome who had some atypical phenotypic

features which overlapped with the DICER1 syndrome. **Material and Methods:** A 17-year-old female presented with a 3-month history of progressive right neck swelling. Fine needle cytology of the thyroid revealed a follicular neoplasm with features suggestive of follicular variant of papillary thyroid carcinoma and she underwent a hemithyroidectomy. Enlarging nodules in the remaining thyroid led to a completion thyroidectomy at 19 years of age. The patient's past medical history included an ovarian mixed malignant germ cell tumour, pulmonary nodules and cysts, renal cysts, mucocutaneous lesions, an arachnoid cyst, and a fibrous breast lesion. Macrocephaly was noted on physical examination. **Results:** Based on the patient's complex phenotype and young age, a hereditary predisposition syndrome was suspected and genetic testing of *PTEN* and *DICER1* was undertaken. A heterozygous truncating germ-line *PTEN* mutation was identified, which combined with clinical findings, met criteria for the diagnosis of Cowden syndrome. Additional loss of heterozygosity of the wild-type *PTEN* allele was detected in the right thyroid lesion and ovarian tumour. No *DICER1* mutations were identified. **Conclusions:** Genetic testing was crucial in elucidating this patient's predisposition to the early development of neoplastic and non-neoplastic conditions. Our report also highlights the phenotypic overlap between the Cowden and DICER1 syndromes and illustrates the importance of recognising the variable phenotypic features of hereditary syndromes in order to enable timely implementation of appropriate care.

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Introduction

Screening for cancer predisposition syndromes is becoming increasingly common practice in modern paediatric oncology and approximately 10% of all paediatric malignancies are attributable to a hereditary predisposition syndrome [1]. Clinically overt thyroid disease is uncommon in childhood and adolescence [2] and clinicians should be suspicious of an underlying genetic aetiology when a child or adolescent presenting with nodular thyroid disease has either a family history of relevant cancers or has already been diagnosed with benign or malignant disease. In these situations, the phenotypic presentation of a patient and relatives must be taken into account to determine the most appropriate genetic test. Patients who harbour a germ-line mutation associated with a cancer predisposition syndrome are at increased risk of developing a specific range of tumours over their lifetime,

and as a result, identifying the correct genetic cause and instituting appropriate counselling and follow-up are necessary.

Here we report a case of an adolescent female with multinodular goitre who had developed multiple tumours, the spectrum of which could be attributed to either *DICER1* or *PTEN* germ-line mutations, highlighting the potential for phenotypic overlap between the conditions associated with these mutations. Of note is that both syndromes are associated with thyroid nodules in younger individuals, as is recognised in the American Thyroid Association's recently published management guidelines for thyroid nodules in children [2].

Material and Methods

Patient

At 17 years of age, a female of Anglo-Saxon descent presented following 3 months of progressive right neck swelling. On examination, there was a soft, non-tender right neck mass, which moved with swallowing. The patient was clinically and biochemically euthyroid. Ultrasound imaging demonstrated multiple nodules in both thyroid lobes, with the largest measuring 39 and 34 mm within the upper and lower poles of the right lobe, respectively (Fig. 1a). Ultrasound-guided fine needle aspiration (FNA) cytology revealed a follicular neoplasm and the patient underwent a right hemithyroidectomy in October 2007. Histopathological examination revealed 2 thyroid nodules (Fig 2a, b). The first was a 35 mm circumscribed nodule with a largely microfollicular, but also focally trabecular and solid growth pattern. In a single section, there were focal areas where nuclei displayed overlapping, angulation, and grooving and some areas featured optically clear nuclei and rare nuclear pseudo-inclusions, in addition to abundant clear cytoplasm. Thick colloid was noted focally. A CK19 immunostain showed patchy, weak immunoreactivity within tumour cells. The findings fell short of criteria needed to make a definitive diagnosis of follicular variant of papillary thyroid carcinoma, and the lesion was reported as a well-differentiated follicular thyroid neoplasm of uncertain malignant potential. In the current terminology of thyroid neoplasms, this tumour would be called a non-invasive follicular neoplasm with papillary-like nuclear features (NIFTP). The second nodule measured 25 mm in diameter and had features of a follicular adenoma. After detailed multidisciplinary review and discussion with the patient, it was elected not to proceed to completion thyroidectomy or radioactive iodine treatment, and close follow-up was instituted, including sonography of the remaining left lobe.

Ultrasound imaging demonstrated multiple enlarging nodules in the left lobe (Fig. 1b), the largest nodule measured 30 × 15 mm and was mixed solid and cystic in appearance. No cervical lymphadenopathy was detected. FNA of the largest nodule was indeterminate, as the sample was heavily bloodstained, limiting assessment. A repeat FNA was offered; however, the patient opted for surgical resection. She underwent a completion thyroidectomy, without prophylactic central neck dissection approximately 2 years following her right hemithyroidectomy.

Fig. 1. Diagnostic imaging. **a** Right thyroid ultrasound showing a 39 mm nodule. **b** Two nodules seen on left thyroid ultrasound, measuring 1.06 and 0.99 cm, respectively. **c, d** Lung cysts (arrows). Pulmonary nodules were also present. **e** Post-therapy whole-body iodine scan (3 GBq): anterior view (left), posterior view (right). The bottom arrow highlights inflammatory lung activity. **f** The SPECT-CT image localises the focal midline iodine activity to a small superior mediastinal lymph node. **g** Left renal cyst indicated

by an arrow. **h** A 7 mm subcutaneous lobulated soft tissue mass detected on the right hand, immediately palmar to the second finger lumbricals. The lesion is hyperintense on the fluid-sensitive sequences and following contrast, and demonstrates moderate homogeneous enhancement. Immediately proximal to the lesion is a nest of mildly prominent vascular structures in keeping with veins. The appearances are consistent with a slow-flow vascular malformation.

Histopathology showed a multinodular architecture with multiple hyperplastic nodules present throughout the entire lobe, as well as focal areas of lymphocytic thyroiditis and a single focus of follicular variant of papillary thyroid carcinoma measuring 4 mm in diameter. Chest computed tomography (CT) performed at the time identified sub-centimetre right pulmonary nodules and right lung cysts (Fig. 1c, d) which remained stable on subsequent serial imaging and were not fluorodeoxyglucose (^{18}F FDG) or iodine-131 avid.

The patient remained under surveillance with ultrasound and serial thyroglobulin (Tg) monitoring without radioiodine ablation. Unstimulated Tg 10 weeks following surgery was 5.0 $\mu\text{g/L}$ (with TSH 6.8 mU/L). A nadir of 0.7 $\mu\text{g/L}$ (with TSH 0.32 mU/L) was achieved 31 months after completion thyroidectomy. Tg remained relatively stable on thyroxine replacement for an additional 3 years (see online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000481620). At 24 years of age

(6.5 years after right hemithyroidectomy) Tg increased to 19 $\mu\text{g/L}$ (with TSH 1.7 mU/L) suggesting recurrent or metastatic thyroid cancer (online suppl. Fig. S1). Ultrasound of the neck 3 months prior to this result had not detected disease in the thyroid bed nor in a cervical lymph node. She had CT of the neck and chest, which revealed a 7 $\times$ 16 mm lymph node in the superior mediastinum. She was staged and treated with 3 GBq of ^{131}I . Post-therapy imaging demonstrated remnant uptake in the left thyroid bed and thyroglossal duct, inflammatory pulmonary activity as well as 2 iodine-avid lymph nodes in the left low cervical (5 mm) and superior mediastinal (13 mm) regions. A repeat CT of her neck and chest 6 months following her ^{131}I showed a radiological response in the superior mediastinal lymph node, which now measured 9 $\times$ 6 mm. On the basis of persistent structural disease evident on CT and a modest dose of 3 GBq at initial therapy, a second dose of 3 GBq radioiodine was given 7 months following the first dose, with only the superior mediastinal lymph node remaining iodine

Fig. 2. **a, b** Thyroid tumour. **a** Encapsulated follicular pattern neoplasm. **b** Nuclear features suggestive of the follicular variant of papillary thyroid carcinoma. **c–f** Ovarian tumour. **c** Low-magnification image mainly showing the yolk sac tumour. The ovary capsule (not involved by the tumour) is seen on the left. **d** Yolk sac tumour. **e** Yolk sac tumour demonstrating AFP immunoreactivity. **f** Choriocarcinoma (syncytiotrophoblast arrowed).

avid (Fig. 1e, f) on post-therapy imaging. The stimulated Tg was 4.4 µg/L (previously 13 µg/L) confirming a partial therapeutic response from the initial dose. Her unstimulated Tg 9 months following the second dose is undetectable (<0.1 µg/L) with a TSH of 0.18 mU/L.

The patient's past medical history included a mixed malignant germ cell tumour of the ovary diagnosed at 3 years of age that mainly exhibited yolk sac and choriocarcinomatous differentiation with more focal embryonal carcinoma and dysgerminoma elements (Fig. 2c–f). A left renal cyst (Fig. 1g), an arachnoid cyst, and mucocutaneous lesions consisting of a cutaneous venous angioma (Fig. 1h) and buccal fibroma were also discovered. A breast lump was detected at 23 years of age. Multiple FNAs and core biopsies were negative for malignancy and comprised predominantly fibrous breast tissue. There was no history of developmental delay. The patient was noted to have macrocephaly with her head circumference measuring 62 cm, 4 cm greater than the 98th percentile.

A cancer predisposition syndrome was not considered at her initial presentation and hemithyroidectomy; however, review of

the clinical phenotype of this young patient at a multidisciplinary meeting prior to radioiodine treatment raised the possibility of Cowden syndrome (CS) as macrocephaly was noted during a clinical review. DICER1 syndrome was also considered in the differential diagnosis due to the presence of thyroid carcinoma in a background of MNG, lung cysts, and a renal cyst.

Genetic testing for germ-line *DICER1* and *PTEN* mutations was undertaken. A heterozygous germ-line pathogenic *PTEN* mutation was identified (c.388C>T; p.Arg130Ter) (online suppl. Fig. S2). Additional loss of heterozygosity (LOH) of the wild-type *PTEN* allele was detected in the ovarian tumour and the right thyroid lesion, consistent with a two-hit tumour suppressor gene inactivation. No LOH of *PTEN* was evident in the left thyroid lesion or breast tissue on Sanger sequencing (online suppl. Fig. S2). Because of the previous identification of *DICER1* RNase IIIb mutations in ovarian germ cell tumours [3, 4] and thyroid carcinomas [5, 6], we sequenced the RNase III domains in each lesion, but no such “hotspot” mutations were identified.

Table 1. Comparison of clinical features exhibited in an adolescent: Cowden versus DICER1 syndromes (designated as common, rare or not reported)

Clinical feature	CS	D1S	Diagnosis (CS or D1S) favoured in this patient
Malignant GCT of the ovary	Rare [15, 16]	Not reported in germ-line mutation carriers; somatic <i>DICER1</i> mutations described ¹ [4]	CS
Thyroid disease			
Nodular hyperplasia	Common [11]	Common [19]	Equally favoured
Differentiated thyroid carcinoma	Reported, frequency uncertain (follicular and papillary variants) [11]	Reported, frequency uncertain (mostly follicular variant of PTC) [5, 6, 19]	Equally favoured
Lung cysts	Rare [12]	Common (septated) [19]	D1S
Renal cysts	Not reported (RCC rather than cysts) [11]	Common (particularly CN; septated) [19]	D1S
Mucocutaneous lesions	Common [11]	Not reported	CS
Breast lesions	Common [11]	Rare ²	CS
Macrocephaly	Common [11]	Common [9]	Slightly favours CS

CN, cystic nephroma; CS, Cowden syndrome; D1S, DICER1 syndrome; GCT, germ cell tumour; PTC, papillary thyroid carcinoma; RCC, renal cell cancer. ¹ It can be challenging to pathologically distinguish between some ovarian tumours; certain non-epithelial tumours are strongly associated to D1S, such as Sertoli-Leydig cell tumours, whereas they are all rare in CS. ² Possibly a coincidental finding [23].

Consent and Sample Review

Consent for this case report was obtained according to institutional ethics procedures. This study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University, Montreal, QC, Canada, No. A12-M117-11A. The patient consented to genetic testing and provided consent to publish. All tumours were reviewed by pathologists (C.J.R.S. and M.P.K.) at the institution from which the samples were acquired and by our central reference pathologist (D.B.-D.S.).

PTEN Screening

Germ-line *PTEN* testing was performed in the standard fashion. The methods used in the genomic DNA (gDNA) and cDNA analyses are described in detail in the online supplementary Materials and Methods. The full *PTEN* coding region and exon-intron boundaries were screened for somatic mutations in gDNA extracted from formalin-fixed paraffin embedded tumour samples. LOH analysis in tumour samples was performed by Sanger sequencing, according to previously published methods [7].

DICER1 Screening

We screened the full *DICER1* coding region and exon-intron boundaries in gDNA extracted from peripheral blood lymphocytes using a custom Fluidigm Access Array followed by next-generation sequencing, as described previously [7]. Large deletions or duplications were screened for using a Multiplex Ligation-Based Probe Amplification assay [8]. Somatic “hotspot” mutations occurring within the regions encoding the *DICER1* RNase IIIa and IIIb domains were screened for by Sanger sequencing, as previously described [5].

BRAF Screening

The region encompassing the *BRAF* c.1799T>A, p.V600E locus was PCR amplified and Sanger sequenced in DNA extracted from the left and right thyroid lesions. Neither of the lesions harboured the *BRAF* hotspot mutation.

Discussion

This case illustrates the complexity and variability of phenotypes associated with tumour predisposition syndromes and the importance of genetic testing in such cases. The constellation of clinical features and tumours observed in this adolescent female were unusual and prompted consideration of an underlying genetic susceptibility. The skin lesions and breast lump were suggestive of CS, whereas the presence of lung and renal cysts led to suspicion of DICER1 syndrome. The macrocephaly and ovarian germ cell tumour favoured CS, but macrocephaly has recently been noted as a feature of the DICER1 syndrome [9] and, in general, non-epithelial ovarian tumours, especially ovarian sex cord-stromal tumours, favour DICER1 syndrome. Thyroid lesions are common features of both DICER1 syndrome and CS. This highlights the overlap between the respective phenotypic

spectra observed in CS and the *DICER1* syndrome (Table 1). Nevertheless, testing of the *DICER1* RNase IIIb domains identified no somatic mutations and, furthermore, no germ-line *DICER1* mutation was present in the patient.

CS is an autosomal dominant predisposition cancer syndrome associated with germ-line mutations in the *PTEN* tumour suppressor gene [10]. *PTEN*, or phosphatase and tensin homologue, is a dual-specificity suppressor phosphatase, whose substrate is a phosphatidylinositol, a phospholipid in the phosphatidylinositol 3-kinase (PI3K) pathway. *PTEN* shares homology with the adhesion molecules tensin and auxilin. A heritable mutation in *PTEN* has been found in 85% of CS patients. *PTEN* mutations have also been detected in 65% of patients with Bannayan-Riley-Ruvalcaba syndrome and 20% of Proteus-like syndrome patients. Considering the overlapping clinical phenotype of these syndromes and their common genetic origin, they are now combined under the umbrella term *PTEN* hamartoma tumour syndrome (PHTS).

The diagnosis of CS is based on several major and minor criteria (outlined in online suppl. Table S1), which were first defined in 1996 by the International Cowden Syndrome Consortium and later revised in 2008 [11]. A clinical diagnosis of CS in an individual can be made based on mucocutaneous lesions alone in sufficient numbers, because of the high prevalence of *PTEN* mutations in adult-onset Lhermitte-Duclos disease (LDD). A diagnosis of LDD alone is also sufficient for a clinical diagnosis of CS. Outside of these pathognomonic criteria, a clinical diagnosis is established with major and minor criteria: 2 or more major criteria of which 1 must be macrocephaly or LDD, 1 major and 3 minor criteria, or 4 or more minor criteria. In the event an individual has a first-degree relative for whom the diagnosis of CS has been made, the criteria are relaxed. Although rare, there are reports of CS patients with lung cysts [12, 13] and ovarian tumours including dysgerminoma [14] and granulosa cell tumour [15, 16]. In the presented case, the patient had macrocephaly and was phenotypically suspected of having CS.

The recently described *DICER1* syndrome is caused by germ-line loss of function mutations in *DICER1* [17] and is inherited in an autosomal dominant fashion. *DICER1* is a member of the ribonuclease III (RNase III) family of proteins and cleaves non-coding small RNA precursors to generate mature microRNAs (miRNAs), which, in turn, post-transcriptionally regulate gene expression. Carriers of *DICER1* mutations are predisposed to devel-

oping a broad range of tumours of predominantly paediatric or adolescent onset [17], as outlined in online supplementary Table S2. The association between *DICER1* syndrome and the majority of these tumours is well established, but since the number of cases with *DICER1* mutations is still limited, new tumoural associations are possible. Notably, although macrocephaly is common and severe in CS [11], it has recently been identified as a surprisingly common feature of the *DICER1* syndrome as well (42% of mutation carriers are macrocephalic) [9]. The patient's ovarian tumour was a malignant germ cell tumour, which would be highly unusual in the *DICER1* syndrome [4]. To our knowledge, no cases of ovarian germ cell tumours have been reported in germ-line *DICER1* mutation carriers. However, there are reports of somatic *DICER1* RNase IIIb mutations in these tumours [3, 4]. Given that the diagnosis of ovarian tumours is often challenging [18], it should be kept in mind that in certain instances, *DICER1* mutation analysis may assist in distinguishing between the types of non-epithelial ovarian cancers [19].

Ultimately, the identification of a heterozygous pathogenic *PTEN* mutation (c.388C>T) in germ-line DNA, combined with LOH of the wild-type *PTEN* allele in the ovarian tumour and right thyroid lesion supported the diagnosis of CS (or PHTS) over *DICER1* syndrome in this patient. This report emphasizes the importance of recognising the variable cancer phenotype associated with *PTEN* mutations, and the possible overlap with other tumour predisposition syndromes, such as the *DICER1* syndrome (and vice versa). The BRAF V600E mutation was not detected in the neoplasms on the right or the left thyroid lobe, as expected. Follicular patterned neoplasms including NIFTPs are not known to harbour BRAF V600E mutations.

Management of this patient was challenging, not least because her original lesion was reported as a follicular neoplasm of uncertain malignant potential. If a hereditary predisposition syndrome had been recognised earlier, it is likely that total thyroidectomy and radioiodine treatment would have been recommended at the age of 17 years. Annual thyroid ultrasound is recommended for surveillance in patients with *PTEN* mutations, because of the risk of thyroid cancer [20, 21], and it has been suggested that prophylactic thyroidectomy may be justified [22], although it is not recommended by the authors. It is thus critical for clinicians to recognize the phenotypic features associated with the different syndromes in order to enable timely implementation of appropriate surveillance. This necessitates the accurate diagnosis of tumours

and the determination of the specific tumour subtype where indicated, as certain tumours/subtypes may be more closely associated with one or other syndrome.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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