Intrathyroidal Thymus (Incidentaloma) Mimicking Thyroid Neoplasia in DICER1 Syndrome

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Established Facts

- Thyroid incidentalomas, i.e., “nonpalpable” thyroid nodules, in children and adolescents are common, and both benign and malignant lesions may be found [1].
- Thymic inclusions and ectopic intrathyroidal thymus with a similar ultrasonographic pattern to papillary thyroid carcinoma should be considered in the differential diagnosis of an apparent thyroid nodule [1, 2].
- Thyroid disease, particularly multinodular goiter (MNG), is the most frequent feature of DICER1 syndrome caused by loss-of-function germline *DICER1* alterations on chromosome 14q32.13; MNG in DICER1 syndrome is usually represented by benign nodules, but thyroid cancer may also occur.

Novel Insights

- Intrathyroidal ectopic thymic tissue can be mistaken for a thyroid nodule and may lead to unnecessary surgery and/or invasive diagnostic procedures in children, especially if it coexists with another organ tumor as observed in DICER1 syndrome.
- Thyroid incidentalomas in DICER1 syndrome patients should be viewed with great suspicion, but not all thyroid disorders are *DICER1*-related in these patients, nor are they necessarily related to a malignant process.

Keywords

Thyroid incidentaloma · Intrathyroidal thymus · DICER1 syndrome

Abstract

Introduction: With the use of ultrasonography for the evaluation of thyroid and nonthyroid neck diseases, the incidental discovery of previously unsuspected thyroid nodules/non-

palpable lesions has increased. Intrathyroidal thymus arises due to aberrant thymic migration during embryogenesis. It is thought to be rare, fulfils the classic criteria for diagnosis of an incidentaloma and it can be mistaken for a thyroid nodule. Multinodular goiter is the main endocrine manifestation of DICER1 syndrome, a tumor predisposition syndrome. Careful thyroid examination including ultrasound is thus necessary for DICER1 syndrome patients. **Case Report:** A 4-year-old prepubertal boy was referred to the pediatric en-

doocrinology department following an earlier diagnosis of pleuropulmonary blastoma (PPB) type III, which is a hallmark component of *DICER1* syndrome. The patient underwent surgery followed by chemotherapy. Genetic analysis identified a germline *DICER1* pathogenic variant (c.2062C>T, p.R688*) in the child and in 5 relatives. A second somatic *DICER1* RNase IIIb hotspot mutation (c.5438A>G, p.E1813G) was identified in DNA extracted from the proband's PPB. He had no goiter on clinical examination, but a heterogenous, well-delineated, avascular, solid and hypoechogenic lesion with pseudomicrocalcifications was observed in the right lobe (4.1 × 3.1 × 2.6 mm), suggestive of thyroid neoplasia. Diagnostic work-up and a 3-year follow-up excluded thyroid neoplasia and confirmed the diagnosis of an intrathyroid benign thymic lesion. **Discussion and Conclusion:** This case exemplifies that thyroid incidentalomas in *DICER1* syndrome patients should be viewed with great suspicion, but that not all thyroid disorders are indeed *DICER1*-related in these patients.

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Introduction

With the use of ultrasonography for the evaluation of thyroid and nonthyroid neck diseases, the incidental discovery of previously unsuspected thyroid nodules/nonpalpable lesions has increased. An intrathyroidal thymus arises due to aberrant thymic migration during embryogenesis, is thought to be rare and it fulfils the classic incidentaloma criteria. The thymus has a unique appearance on ultrasonography, and ectopic thymus parenchyma can be easily identified by an experienced pediatric radiologist or endocrinologist. Diagnosis and follow-up of ectopic intrathyroidal thymic tissue can be performed non-invasively by thyroid ultrasound.

Ectopic juvenile intrathyroidal thymus presents as a solid and hypoechogenic area, with regular and sharp margins and no blood flow on power/color Doppler examination [1]. The thymus undergoes a process called involution, which is defined as a decrease in the size and weight of the gland with advancing age. During involution, the epithelial component undergoes atrophy, resulting in small scattered lymphocytes in abundant adipose tissue [3]. Ectopic thymus during involution appears as an hypoechogenic area with multiple hyperechogenic dots (microcalcification-like), and similar tissue is observed usually below the thyroid lower poles where the thymus is located [1]. Hyperechogenic dots observed in intrathyroidal ectopic thymus are pseudomicrocalcifications and can be

Fig. 1. a Pedigree of the family shows a remarkable family history. **b** Chromatograms show the germline *DICER1* variant, c.2062C>T, p.R688* (panel I) and the somatic *DICER1* mutation, c.5438A>G, p.E1813G, identified in the pleuropulmonary blastoma (PPB) (panel II). MNG, multinodular goiter.

mistaken for the true microcalcifications (<2 mm in diameter/size) observed in papillary thyroid microcarcinoma (mPTC) or medullary thyroid microcarcinoma (mMTC), thereby leading to a stressful clinical situation for the patient and physician. Intrathyroidal ectopic thymic tissue can thus be mistaken for a thyroid nodule and may lead to unnecessary surgery and/or invasive diagnostic procedures in children due to the overlap of its appearance with mPTC or mMTC on ultrasound. The widespread use of thyroid ultrasound in children can result in an increased detection rate of thymic inclusions, and, as such, ectopic intrathyroidal thymus should be considered in the differential diagnosis of an apparent thyroid nodule in children and adolescents [2].

Pleuropulmonary blastoma (PPB) is a hallmark component of *DICER1* syndrome and diagnosis should prompt surveillance for other *DICER1* syndrome-related disorders including multinodular goiter (MNG), cystic nephroma, pituitary blastoma, Sertoli-Leydig cell tumor, cervical embryonal rhabdomyosarcoma, and others [4–6]. The phenotypic spectrum of *DICER1* syndrome is broad, but, apart from MNG, it generally includes rare-to-very-rare entities

showed no change in the lesion size despite the patient's advancement in age, supporting the diagnosis of an ectopic thymus undergoing involution (Fig. 2a) but mimicking in part a true thyroid cancer in another patient (Fig. 2d).

Discussion

The increasing use of thyroid ultrasound for children may lead to a rise in the detection of thymic inclusions, and ectopic intrathyroidal thymus should be considered in the differential diagnosis of an apparent thyroid nodule in children and adolescents [1, 2, 12]. The thymus has a unique appearance on ultrasonography and ectopic thymus parenchyma can be easily identified. Diagnosis and follow-up of ectopic intrathyroidal thymic tissue can be performed noninvasively by thyroid ultrasound. The tissue may be considered substantially benign and self-limited if no change in size is observed over a period of months/years; rarely, a small increase in size may be related to the normal growth of the thymus during development. In older patients, thymic inclusions exhibit a decrease in size and an increase in echogenicity, and the margins of the lesions become less defined, most likely reflecting normal thymus involution that occurs with advancing age and involves the atrophy of the epithelial component, resulting in small scattered lymphocytes in abundant adipose tissue [1, 2, 12]. To the experienced examiner, the appearance of thymic tissue is pathognomonic on ultrasound and is associated with stability or regression at follow-up. The prevalence of ectopic thymus detected incidentally in children who underwent neck or thyroid ultrasonography was 2.3% (16/690) [13], lower than the previously reported 3.9% (7/180) [14] and 17.3% (9/52) [15]. This wide range in prevalence may have largely been due to the number of patients examined in each study. A prevalence of 8% of ectopic thymus occurring in young children with congenital hypothyroidism related to thyroid dysgenesis was reported [16]. For these patients, abnormal thymus development coexisted with a thymus in its normal location. The regression of intrathyroidal thymic inclusions can be safely monitored by ultrasound, thus avoiding invasive fine-needle aspiration biopsy (FNAB) or surgery. Tumors arising from the ectopic thymus are extremely rare and can also be monitored by ultrasound [12].

Despite the diagnosis of DICER1 syndrome in our patient, invasive diagnostic workup (FNAB under anesthesia) and surgical intervention of the thyroid incidentaloma were not indicated. We previously reported the case of a young patient whose parent had MEN2A [1]. The child

was found to have an intrathyroidal ectopic thymus. The patient was negative for the *RET* mutation found in a parent, but concern led to full *RET* sequencing, which was negative. Thus, presence of the new thyroid lesion in this patient generated doubt as to whether the genetic testing result was correct and resulted in unnecessary additional genetic testing.

In the same vein, based on long-term experience in pediatric thyroid ultrasound, the diagnosis of ectopic thymic residue in the child with DICER1 syndrome was made in the absence of cytological and molecular tests that would necessitate invasive FNAB under general anesthesia. The appearance of the lesion was strongly consistent with intrathyroidal thymus on ultrasound, but indolent mPTC was not ruled out explicitly. The lack of enlargement over time also does not fully exclude mPTC. Ito et al. [17] showed the data of 1,235 patients with subclinical low-risk mPTC over an average observation period of 75 months. The rate of incidence of enlargement at the 5- and 10-year observations in this study was 4.9 and 8.0%, respectively. Enlargement of mPTC in the youngest population (<40 years of age) at 5 years was noted in only 9.1% of the participants. In the remaining 90.9%, the size of the mPTC remained unchanged. Unfortunately, such data on children <10 years of age are not available in the literature. The prevalence of ectopic intrathyroidal thymus in children is relatively high, in contrast to the extremely rare occurrence of microcancer in this age group. Despite this, it should be borne in mind that thyroid ultrasonography is not a test to confirm or exclude thyroid cancer. In summary, the case presented here exemplifies that thyroid incidentalomas in DICER1 syndrome patients should be viewed with great suspicion, but that not all thyroid disorders are *DICER1*-related in these patients.

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Statement of Ethics

This study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University, Montreal, QC, Canada (Nos. A12-M117-11A and A08-M61-09B) and the Bioethical Commission on Human Research, Poznan University of Medical Sci-

ences, Poznan, Poland (Nos. 257/01 and 258/01). Participants were recruited to the study in compliance with the second edition of the Canadian Tri-Council Policy Statement of Ethical Conduct of Research Involving Humans. The parents of subjects gave their written informed consent to publish the cases (including any images).

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

M.N. performed the clinical examination, referred the patient for genetic testing, conceived the study, and wrote the manuscript. N.S. performed the *DICER1* genetic testing. L.d.K. assisted with genetic testing and the writing of the manuscript. W.D.F. oversaw the *DICER1* genetic testing and reviewed the manuscript.