J Ped Surg Case Reports 11 (2016) 31–34

Contents lists available at ScienceDirect

Journal of Pediatric Surgery CASE REPORTS

journal homepage: www.jpscasereports.com

DICER1 syndrome and thyroid disease

Michael Canfarotta [a,1], Rebecca Riba-Wolman [b,2], Andrea D. Orsey [c,3], Fabiola Balarezo [d,4], Christine Finck [e,*]

[a] University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06032, USA
[b] Department of Pediatrics and Endocrinology, Connecticut Children's Medical Center, Multidisciplinary Thyroid Center, 282 Washington Street, Hartford, CT 06106, USA
[c] Department of Pediatrics and Hematology/Oncology, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106, USA
[d] Department of Pathology and Laboratory Medicine, Hartford Hospital, 80 Seymour Street, P.O. Box 5037, Hartford, CT 06102, USA
[e] Department of Surgery, Connecticut Children's Medical Center, Multidisciplinary Thyroid Center, 282 Washington Street, Hartford, CT 06106, USA

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form
25 May 2016
Accepted 26 May 2016

Key words:
DICER1
Multinodular goiter
Ovarian Sertoli-Leydig cell tumor
Cancer predisposition syndrome
Pediatric onset tumors

ABSTRACT

DICER1, a member of the ribonuclease III (RNase III) family, is known to play an important role in the post-transcriptional regulation of gene expression and germline mutations have been associated with a familial tumor susceptibility syndrome. In this report, we describe an 11-year-old female with a history of ovarian Sertoli-Leydig cell tumor resection and known DICER1 mutation (c.325C>T, p.Gln109*). She presented with multiple thyroid nodules on screening ultrasound. On fine needle aspiration she was found to have cytologic atypia, which in the general adult population confers a 5–15% risk of malignancy. Herein, we review the literature on DICER1 phenotype and pediatric thyroid disease and discuss management options.

DICER1 is a member of the ribonuclease III (RNase III) family that is involved in cleaving double stranded pre-microRNAs into mature micro-ribonucleic acids (miRNAs) [1]. Mature miRNAs are 22 nucleotide, single stranded, noncoding small RNAs that bind to the 3′-untranslated region of target mRNAs to suppress their translation by either silencing or degradation [2]. These molecules regulate the expression of many cellular proteins. Dysregulation of miRNAs has been related to cancer initiation and progression for several tumor types, including all variants of thyroid cancer [2]. DICER1 germline mutations also have been described in association with multinodular goiter (MNG), Sertoli-Leydig cell tumors (SLCT), cystic nephroma, pleuropulmonary blastoma, primitive neuroectodermal tumor, cervical embryonal rhabdomyosarcoma, and Wilms tumor [3–10]. We present a pediatric case of MNG with atypia of undetermined significance on fine needle aspiration (FNA) in a patient with a history of ovarian SLCT and confirmed DICER1 syndrome and review the literature on work up and management.

1. Case report

An 11-year-old female presented with nine nodules, the largest being 1 × 0.8 × 0.9 cm (Fig. 1), on her thyroid screening ultrasound following confirmation of a DICER1 mutation (c.325C>T, p.Gln109*).

Four years previously, she was diagnosed with SLCT of the right ovary. She underwent an oophorectomy and completed chemotherapy including six cycles of PEB (cisplatin, etoposide and bleomycin) as per AGCT0132. She did not receive radiation therapy. She developed autoimmune hypothyroidism shortly after treatment for her SLCT and had been maintained on levothyroxine. She had no family history of thyroid disease and no complaints suggestive of hyper or hypothyroidism while on levothyroxine. Her physical exam was unremarkable with no palpable thyroid nodules or cervical adenopathy. The patient underwent FNA biopsy of the thyroid nodules, which demonstrated atypia of undetermined significance (Bethesda class III). With the reported 5–15% risk for malignancy, case reports of differentiated thyroid cancer in DICER1

* Corresponding author. Tel.: +1 860 545 9520; fax: +1 860 545 9545.
E-mail address: cfinck@connecticutchildrens.org (C. Finck).
[1] Tel.: +1 860 679 7845; fax: +1 860 679 1201.
[2] Tel.: +1 860 837 6700.
[3] Tel.: +1 860 545 9630.
[4] Tel.: +1 860 972 2249.

http://dx.doi.org/10.1016/j.epsc.2016.05.014

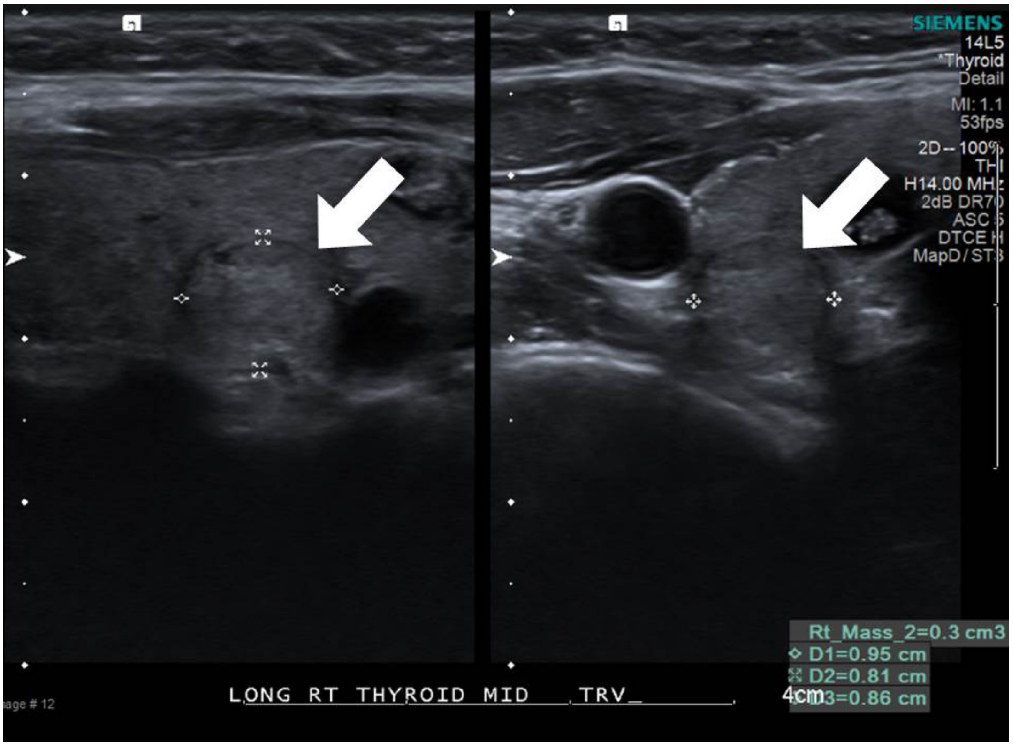

Fig. 1. Ultrasound of the thyroid shows an isoechoic nodule measuring 1 × 0.8 × 0.9 cm (white arrows) in the presence of multiple smaller nodules bilaterally (not depicted).

mutations, and the challenges of monitoring multiple nodules as well as anticipated anxiety associated with repetitive screening in a patient with prior cancer, the family opted for total thyroidectomy. Intraoperative pathologic examination showed multiple, well-circumscribed hyperplastic nodules with some nodules showing cellular atypia. However, these nodules were not diagnostic for a follicular variant of papillary carcinoma and most consistent with MNG (Fig. 2).

2. Discussion

The familial tumor susceptibility syndrome associated with germline inactivating mutations in DICER1 has only been recognized for the past several years [3]. Heterozygous germline DICER1 mutations, usually in the context of a tissue-specific mutation on the other allele, predispose to various tumors, collectively called DICER1 syndrome [11]. Pleuropulmonary blastoma and SLCT are two of the characteristic tumors of DICER1 syndrome [11]. In fact, early results from the International Ovarian and Testicular Stromal Tumor Registry show germline DICER1 mutations in 48% of girls and women with SLCT [12]. The exact prevalence of DICER1 mutations is unknown but it is assumed to be a rare condition that is characteristically inherited in an autosomal dominant manner with variable penetrance. Genetic counseling is recommended as each child of an individual with a pathogenic variant of the gene has a 50% chance of inheriting the variant [13]. To date, nearly fifty different germline mutations with various neoplasms have been reported that include nonsense, frameshift, splicing, and missense mutations along with large gene rearrangements [3–10,14–17].

Our report describes a young female previously diagnosed with ovarian SLCT that underwent molecular testing confirming a DICER1 mutation. Several years later the phenotype expanded with presentation of MNG. The prevalence of MNG is reportedly between 3.9% and 6% in school-age children and adolescents and most frequently associated with chronic lymphocytic thyroiditis [18]. However, in DICER1 syndrome, MNG has been reported to occur along with differentiated thyroid cancer [11]. Additionally, the FNA of our patient demonstrated atypia of undetermined significance (Bethesda class III), thus raising concern for possible malignancy. The new American Thyroid recommendations in adults suggest lobectomy or repeat FNA in this setting [19]. However, the

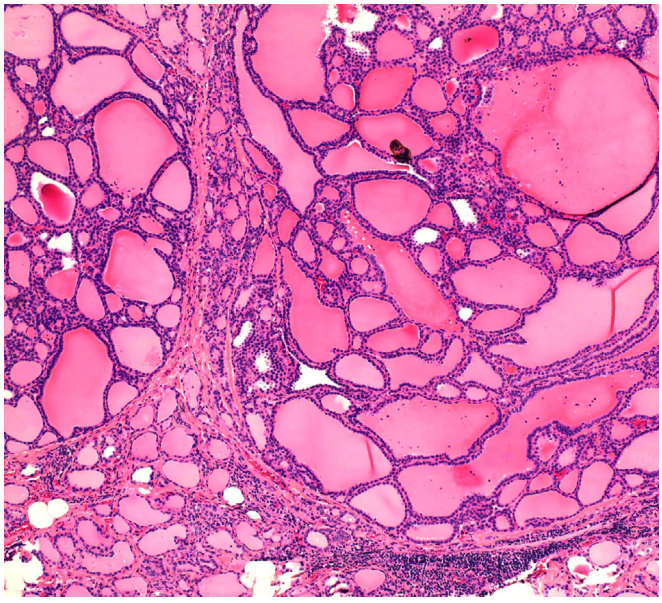

Fig. 2. Thyroid tissue with hyperplastic/adenomatoid nodules, H&E, ×100.