Ectopic Thymus Presenting as a Thyroid Nodule in a Patient with the Carney Complex

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Ectopic thymic tissue within the thyroid gland is rare. Patients with a complex of myxomas, spotty skin pigmentation, and endocrine overactivity, collectively known as Carney complex (CNC), have a predisposition towards the development of thyroid abnormalities, but there are no reports of thymic defects in CNC. We present the case of a 12-year-old boy with CNC and a growing thyroid nodule. The patient had the c.682 C > T (Arg228X) pathogenic *PRKARIA* mutation. Hemithyroidectomy for a Hürthle cell adenoma led to the confirmation of distinct intrathyroidal ectopic thymic tissue. Thymic abnormalities have not been previously reported in CNC.

Introduction

THE COMPLEX OF spotty skin pigmentation, myxomas, and endocrine overactivity, or Carney complex (CNC), is a multiple neoplasia and lentiginosis syndrome (1–4) that is inherited in an autosomal dominant manner (5). The condition is genetically heterogeneous (6–8), the majority of the cases being caused by mutations in the gene coding for the protein kinase A regulatory subunit type 1A (*PRKARIA*) (4,7,8). In addition to those lesions that constitute part of the classical diagnostic criteria of the syndrome (4), patients with CNC may be predisposed to several other conditions, including a variety of cancers and possibly developmental defects (9). The latter occurs in other forms of inherited multiple endocrine neoplasias and hamartomas, noncancerous disorders such as Cowden syndrome (10), conditions with which CNC shares several features (11). CNC endocrine manifestations include primary pigmented nodular adrenocortical disease, growth hormone-producing pituitary adenomas, testicular tumors, and various thyroid lesions (9,12–14). The testicular lesions include large-cell calcifying Sertoli cell tumors (15), adrenocortical nodular rests, and Leydig cell tumors (1,9).

Subject and Methods

Case report

The patient and his family members were enrolled in protocol 95-CH-0059 for the genetic investigation of CNC-

related tumors; the patient signed an assent form and his mother a consent form. The study and all forms have been approved by the institutional review board of the National Institute of Child Health and Development. The patient, a 12-year-old boy, diagnosed with CNC at age 7 years because of bilateral large-cell calcifying Sertoli cell tumors and a family history of CNC, presented with an enlarging thyroid nodule. Thyroid function tests were normal. Ultrasonography demonstrated a 6-mm solid hypoechoic thyroidal nodule and a second hypoechoic lesion; serial ultrasound studies over the course of a year showed an increase in size of the first lesion; a fine needle aspiration revealed Hürthle cells suggestive of a Hürthle cell neoplasm, and reactive lymphoid elements and epithelial-like cells that, based on cytological along with immunocytochemical and flow cytometric findings, were suggestive of ectopic thymic tissue. The patient underwent right hemithyroidectomy. The patient's 45-year-old mother was diagnosed with CNC at the age of 27 years and is undergoing treatment for metastatic undifferentiated thyroid carcinoma.

DNA and fluorescent in situ hybridization (FISH) analysis

Genomic DNA was obtained from thyroid tissue and peripheral blood from the patient and his mother. Cells for FISH were harvested from the excised surgical specimen. Direct bidirectional sequencing was employed to analyze all coding

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FIG. 1. (A) Circumscribed, cystic lesion in a background of normal thyroid parenchyma, epithelial component was present at one margin of the lesion. (B) High power view of epithelial component in A showed a compressed follicular lesion composed of cells with empty eosinophilic cytoplasm (Hürthle cells) surrounded by a fibrous capsule. (C) Fluorescent *in situ* hybridization with a *PRKAR1A*-containing probe showed allelic losses: all cells that are shown have one signal instead of the expected two for the chromosome 17q22-24-located *PRKAR1A*; (D) Ultrasonography showed a lesion that immunostainically was ectopic thymus; (E) Thymic tissue (in the square) (hematoxylin and eosin, $\times 5$), the thyroid gland shows mild nodularity.

regions and the flanking exon/intron junctions of the *PRKAR1A* gene and FISH employing a *PRKAR1A*-containing probe were completed by standard methods (7,8).

Results

Imaging and histologic findings

Histologically, the 6-mm cystic nodule seen on ultrasonography corresponded with Hürthle cell nodule (Fig. 1A, B). The tumor cells had allelic losses of the *PRKAR1A* gene (Fig. 1C) but the lesion had no features of malignancy and surrounding lymph nodes were normal. The patient is presently euthyroid (10 years follow-up). Serial ultrasonography of the left lobe is normal (data not shown).

The smaller hypoechoic lesion was normal (ectopic) thymus (Fig. 1E), consistent with fine needle aspiration findings (Fig. 2). Lymphoid cells were CD-3 and CD-8 positive upon immunoperoxidase staining; the thyroglobulin-negative staining in epithelial appearing cells (data not shown) confirmed the thymic nature of the lesion within the thyroid.

DNA analysis

DNA sequencing revealed the presence of the c.682 C > T (Arg228X) pathogenic *PRKAR1A* mutation in the heterozy-

gote state in both the patient's peripheral blood and thyroid tissue-derived DNA (data not shown). The patient's mother (CAR110 kindred) had the same mutation (7,8).

Discussion

Thymus is derived from both ectoderm and endoderm of the third and often the fourth branchial clefts and pharyngeal pouches along with the thyroid and parathyroid glands (16,17). During the sixth week of gestation, the epithelium of the third pharyngeal pouch differentiates into the inferior parathyroid and the thymus; the epithelium of the elongated ventral parts of the third pair of pouches proliferates and forms cavities (17). The bilateral primordia of thymic tissue migrate to the median plane, form the definitive thymus which then descends into the superior mediastinum (16,17). Ectopic thymic tissue may be located along this pathway from the angle of mouth or base of the skull to the superior mediastinum (18–21). Aberrant thymic tissue may be found in the neck of up to 20% of the general population (16,17) but intrathyroid ectopic thymic tissue is exceedingly rare and is usually found incidentally (18). Interestingly, in pediatric necropsies, ectopic thymic tissue is quite often associated with congenital heart disease (18).

FIG. 2. Polymorphous population of lymphocytes and epithelial-like cells seen in the aspirate and shown to represent ectopic thymic tissue (Diff-Quik, 120X).

Intrathyroidal ectopic thymic tissue is rarely symptomatic and is often interpreted as Hashimoto's thyroiditis or lymphoma of the thyroid when evaluated by fine-needle aspiration (16,18–21). Differential diagnosis of intrathyroidal and/or cervical thymomas should include related tumors of thymic or branchial pouch origin, such as hamartomatous thymomas, spindle epithelial tumors with thymus-like differentiation, and carcinoma showing thymus-like differentiation (20). On ultrasonography, intrathyroid thymic tissue may present as a solid thyroid nodule without specific characteristics (19,21).

By ultrasonography, up to 75% of patients with CNC have been found to have cystic or multinodular thyroid disease (9,13). On biopsy, follicular adenoma is the most common finding, but thyroid cancer (papillary or follicular) may develop in up to 10% of CNC patients (13). This is consistent with *PRKAR1A* loss of function mutation in sporadic thyroid tumors (22). However, patients with CNC are not known to develop any thymic lesions. The association of the latter with congenital heart disease (18) is interesting because *PRKAR1A* deficiency does indeed cause heart defects in mice (23) and rarely in humans (9).

In conclusion, we report a patient with CNC and ectopic intrathyroid thymic tissue, an observation that has not been made before. It remains to be seen whether this is a rare and coincidental finding or a defect related to *PRKAR1A* haploinsufficiency.

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Disclosure Statement

The authors report no conflicts of interest.

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