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RAS Mutation-Positive Follicular Variant of Papillary Thyroid Carcinoma Arising in a Struma Ovarii

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Abstract Struma ovarii is an ovarian mature teratoma composed exclusively or predominantly of thyroid tissue. Malignant transformation of struma ovarii is rare and poorly understood, although this process is thought to be similar to carcinogenesis in malignant tumors of differentiated thyroid tissue originating in the thyroid gland. Genetic alterations in the mitogen-activated protein kinase pathway, including mutations of *BRAF*, *RAS*, and *RET* genes, have been implicated in the development of differentiated thyroid carcinoma arising in the thyroid gland. We report here a case with *RAS* mutation detected in a malignant struma ovarii. The patient is a 38-year-old female who had a 2.4 cm ovarian cyst noted incidentally on a first trimester ultrasound. She proceeded to ovarian cystectomy post-delivery, with pathologic examination detecting a papillary thyroid carcinoma, follicular variant, arising in a cystic teratoma. The tumor was tested for *BRAF*, *RAS*, and *RET/PTC* mutations. *HRAS* codon 61 mutation was identified. This is the first report of *RAS* mutation detected in the follicular variant of papillary carcinoma arising in a struma ovarii. It provides evidence that tumors developing in this setting involve molecular mechanisms similar to those implicated in tumors developing in the thyroid gland.

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Introduction

Struma ovarii is a type of ovarian teratoma where the major cellular component (>50%) of the tumor mass is thyroid tissue. Approximately 3% of ovarian teratomas are of this type, making struma ovarii the most common type of monodermal teratoma [1].

Struma ovarii is most commonly diagnosed in women in their 50's, although cases occurring before puberty and after menopause have been reported [1]. While often identified incidentally on imaging studies, approximately one third of struma ovarii patients can present with ascites or Meigs' syndrome (the triad of ovarian tumor with ascites and pleural effusion that resolves after resection of the tumor). Thyrotoxicosis from functional ectopic thyroid tissue occurs in about 5–15% of cases [2]. Although in general, benign, malignant transformation of the tumor is reported in 0.1–0.3% of cases [3]. Overall prevalence estimates are confounded by the fact that reports of malignant struma ovarii in the older literature may actually have been examples of strumal carcinoid. It has even been suggested that the term "malignant struma ovarii" be dropped in favor of a more precise description such as "thyroid-type carcinoma originating in struma ovarii" [1].

Rare cases of differentiated thyroid cancer metastatic to the ovary have been reported [4, 5]. Such cases differ diagnostically from struma ovarii containing thyroid-type carcinoma in the fact that mature cystic teratoma component is not present, and the patients almost invariably have a prior history of thyroid cancer.

The most frequent type of thyroid malignancy is papillary carcinoma, which constitutes approximately 80%

of all cases. Papillary carcinomas frequently have genetic alterations leading to the activation of the mitogen-activated protein kinase (MAPK) signal pathway. Those include *RET/PTC* rearrangement and point mutations of the *BRAF* and *RAS* genes. These mutations are found in approximately 70% of all cases and rarely overlap in the same tumor [6–8]. Point mutations of the *BRAF* serine/threonine kinase are the most common genetic event in sporadic papillary carcinomas, being found in approximately 45% of these tumors [6, 9]. Virtually all mutations in thyroid carcinomas involve nucleotide 1799 and result in a valine-to-glutamate substitution at residue 600 (V600E). The *RET* receptor tyrosine kinase gene is activated by rearrangements known as *RET/PTC* [10]. It results in fusion of the 3′ portion of the *RET* gene to the 5′ portion of various genes. Two most common rearrangement types, *RET/PTC1* and *RET/PTC3*, are paracentric inversions since both *RET* and its respective fusion partner, *H4* or *ELE1* (*NCOA4*), reside on the long arm of chromosome 10 [10–12]. The prevalence of *RET/PTC* in papillary carcinomas is approximately 20%, has significant geographic variation, and is higher in tumors from patients with history of radiation exposure and in pediatric populations [13]. Another type of genetic alteration in papillary carcinomas is *RAS* point mutations, which involve several specific sites (codons 12, 13, and 61) of *NRAS*, *HRAS*, or *KRAS* genes, and are found in 10–15% of tumors [14–16]. Papillary carcinomas harboring *RAS* mutation almost always have the follicular variant histology [16, 17].

There have been few studies of the genetic alterations in malignant struma ovarii. The molecular changes involved in malignant transformation in struma ovarii are poorly understood, although are thought to parallel similar changes leading to the development of thyroid cancer developing in the thyroid gland proper. *BRAF* mutations have been reported in both malignant struma ovarii [18] and PTC [19]. We believe the following case report to be the first described case of a *RAS* mutation in a malignant struma ovarii.

Case Description

The patient is a 38-year-old female who had an ovarian cyst incidentally noted on a first trimester ultrasound. A subsequent pelvic ultrasound showed features suggestive of a left ovarian cystic teratoma measuring at 2.4×2.2×2.1 cm. (Fig. 1). The patient was biochemically euthyroid with a thyroid-stimulating hormone of 1.666.

The patient delivered her first child without complications and proceeded to ovarian cystectomy. Gross examination revealed a partially collapsed 2.8 cm cyst containing soft gray tan pasty material. An area of ossification was noted measuring 0.6 cm. Microscopic examination identified a papillary thyroid carcinoma, follicular variant, arising in a mature cystic teratoma (Fig. 2). Other tissue components of the cystic teratoma included adipose tissue, cartilage, bone, and skin.

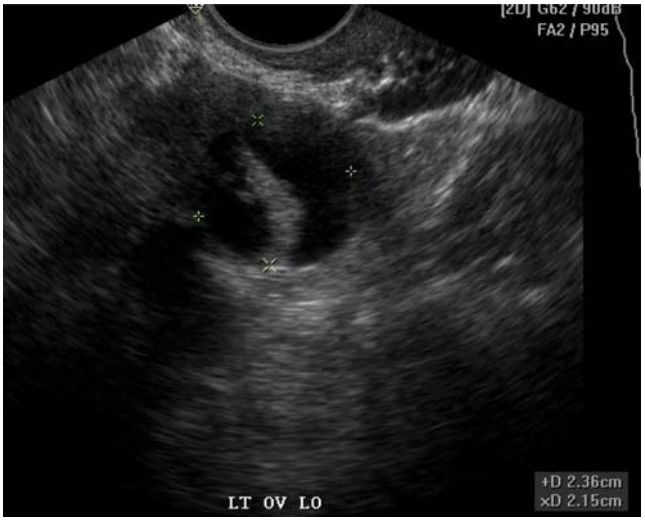

Fig. 1 Ultrasound (u/s) image of left ovarian mass showing a 2.4×2.2×2.1 cm complex left ovarian cyst with internal septation

The tumor tissue was tested for *RET/PTC1* and *RET/PTC3* rearrangements by fluorescence in situ hybridization, and for *V600E BRAF* mutation and three most common *RAS* point mutations found in thyroid cancer, *NRAS* codon 61, *HRAS* codon 61, and *KRAS* codon 12/13 using polymerase chain reaction and fluorescent melting curve analysis on LightCycler as previously described [16]. No *BRAF* mutation or *RET/PTC* rearrangement was found, but the tumor DNA revealed *NRAS* codon 61 mutation CAG→AAG corresponding to gln→lys amino acid change (Fig. 3).

Thyroid ultrasound and neck computed tomography were completed and found to be normal. After reviewing available treatment options, the patient elected no further treatment at this time, with plans for a final pregnancy and then thyroidectomy followed by radioactive iodine whole body scanning and ablation.

Discussion

The differential diagnosis of monodermal germ cell tumors includes struma ovarii and strumal carcinoid. Strumal carcinoid generally presents as a unilateral ovarian mass with histologic examination revealing gastrointestinal or respiratory epithelium present within a cystic teratoma [20]; the carcinoid syndrome can be present in up to one third of patients due to direct venous drainage of the tumor.

The pathogenesis of thyroid carcinoma arising in struma ovarii remains poorly understood. Very little is known

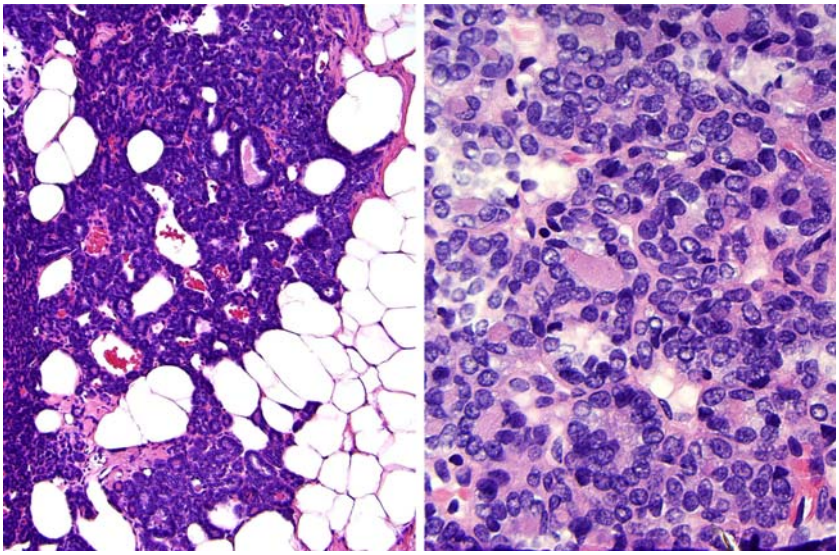

Fig. 2 Microscopic images of papillary carcinoma. *Left*: the tumor shows a predominantly microfollicular growth pattern and an infiltrative border. *Right*: high power view of the tumor showing small follicles lined by cells with overlapping nuclei showing features characteristic of papillary carcinoma

about molecular profiles of these tumors. In one report, *BRAF* mutation has been identified [4], suggesting that similar genetic alterations may be responsible for thyroid tumors developing at this ectopic site. No *RAS* mutations or *RET/PTC* rearrangements have been reported in these tumors. This study represents to our knowledge the first report of *RAS* mutation identified in a papillary carcinoma arising in ectopic thyroid tissue of struma ovarii. In striking similarity with papillary carcinomas developing in the thyroid gland, this mutation was also associated with the follicular variant histology of the tumor.

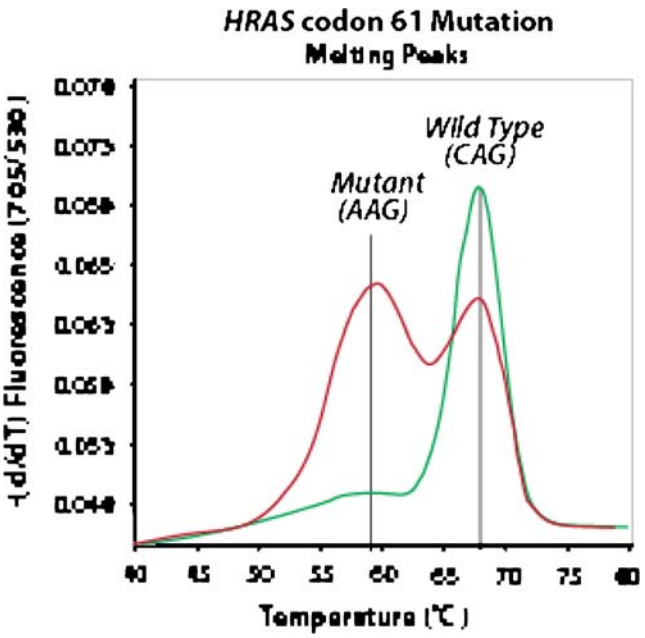

Fig. 3 Detection of *HRAS* codon 61 point mutation in the tumor by real-time polymerase chain reaction (PCR) amplification and melting curve analysis. The negative control (normal thyroid) shows one wild-type melting peak at 67.6°C (*green*), whereas the tumor sample (*red*) demonstrates two melting peaks, one corresponding to the wild-type sequence with T_m of 67.6°C and another at T_m of 59°C corresponding to the mutant sequence. Subsequent sequencing analysis of the PCR products identified the CAG to AAG mutation at codon 61

The *RAS* genes (*HRAS*, *KRAS*, and *NRAS*) encode highly related G-proteins that play a central role in the intracellular transduction of signals arising from cell membrane receptors [21]. In its inactive state, RAS protein is bound to guanosine diphosphate (GDP). Upon activation, it releases GDP and binds guanosine triphosphate (GTP), activating the MAPK and other signaling pathways, such as PI3K/AKT. Normally, the activated RAS-GTP protein becomes quickly inactive due to its intrinsic guanosine triphosphatase (GTPase) activity and the action of cytoplasmic GTPase-activating proteins. Point mutations in the discrete domains of the *RAS* gene either increase its affinity for GTP (mutations in codons 12 and 13) or inactivate its autocatalytic GTPase function (mutation in codon 61). As a result, the mutant protein becomes permanently switched in the active position and continuously activates its downstream targets. Mutations of all three genes have been reported in thyroid cancer [22] and represent one of the most frequent genetic alterations identified in spontaneous epithelial thyroid tumors. Single-base substitutions leading to constitutive protein activation and cell proliferation have been reported [20]. *NRAS* mutations also have been examined as a prognostic factor for aggressive behavior in human papillary thyroid carcinoma [26].

In thyroid tumors, point mutations of *RAS* occur with variable frequency in all types of thyroid follicular cell-

derived tumors, including papillary carcinoma and follicular carcinoma. In papillary carcinomas, *RAS* mutations are found in 10–15% of tumors [14, 15]. Mutations involving *NRAS* codon 61 and *HRAS* codon 61 are most common, although mutations have been found in different hotspots of all three genes. Of interest, papillary carcinomas with *RAS* mutations arising in the thyroid gland almost always have the follicular variant histology [16, 17].

The finding in this study indicates that pathogenesis of papillary carcinoma that develops in struma ovarii is similar to those tumors arising in the thyroid gland. Moreover, similar to the latter, *RAS* mutations in these tumors appears to also be associated with the follicular variant of papillary carcinoma. Future studies of the effects of *RAS* mutations may provide clues to the pathogenesis of this type of tumor variant arising in struma ovarii.

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