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Synchronous Independent Papillary Thyroid Carcinomas in Struma Ovarii and the Thyroid Gland With Different *RAS* Mutations

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Struma ovarii is a rare ovarian teratoma predominantly composed of thyroid tissue. The simultaneous presence of thyroid carcinoma in the struma ovarii and the thyroid gland is extremely rare. It remains unclear if these carcinomas represent independent primary tumors and whether the molecular mechanisms of the tumors developing in the thyroid and ovarian tissues are similar. We present the case of a patient with two independent papillary thyroid carcinomas (PTCs) in struma ovarii and the thyroid gland that are driven by different *RAS* mutations. A 62-year-old woman with a history of chronic lymphocytic leukemia/small lymphocytic lymphoma was diagnosed with a pelvic mass during a CT scan. She had surgery that included removal of her ovaries. A 7.2-cm classical variant of PTC arising in a struma ovarii was identified in the right ovary. Two months after the pelvic surgery, total thyroidectomy was performed, and a small nodule (0.8 cm) in the left lobe was diagnosed as a classical variant of PTC. Molecular analysis of tissues obtained from both the malignant struma ovarii and thyroid gland was performed. *RAS* mutations both in the PTC located in the thyroid and ovarian tissues were identified. However, whereas the thyroid gland tumor showed an *HRAS* Q61R mutation, the PTC in struma ovarii harbored an *NRAS* Q61R mutation. In this case, the finding of distinct types of *RAS* point mutation in thyroid cancers at two different locations provides definitive evidence that these cancers are synchronously developed independent primary tumors.

Freeform/Key Words: point mutation, PTC, *RAS*, struma ovarii, thyroid cancer

Struma ovarii is a rare ovarian teratoma predominantly composed of thyroid tissue. The occurrence of malignant struma ovarii is rare, corresponding to <10% of ovarian strumas [1]. The coexistence of papillary thyroid carcinoma (PTC) not only in the struma ovarii but also in the thyroid is extremely unusual, with few reports in the literature [2, 3]. Very little is known about the molecular mechanisms of these tumors and whether the thyroid and ovarian tissues harbor the same abnormalities and thus have similar mechanisms of development and progression. Although a few previous studies have described somatic mutations of malignant struma ovarii [3, 4], to our knowledge, no study has described concomitant somatic mutations in PTC in the struma ovarii and thyroid. We present the case of a patient with two independent PTCs in struma ovarii and the thyroid gland that are driven by different *RAS* mutations.

Abbreviations: CLL, chronic lymphocytic leukemia; PTC, papillary thyroid carcinoma; SLL, small lymphocytic lymphoma; Tg, thyroglobulin.

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1. Patient and Methods

A 62-year-old woman was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in 2008 due to chest, abdominal, and pelvic lymphadenopathy. She was asymptomatic and did not receive any chemotherapy or radiotherapy. In February 2013, a routine follow-up CT scan identified a solid pelvic mass. A year before, the CT scan had demonstrated only stable enlarged pelvic lymph nodes. In April 2013, she had surgery that included removal of her ovaries. A 7.2-cm classical PTC arising in a struma ovarii was identified in the right ovary [Fig. 1(a) and 1(b)].

She was referred to the Endocrinology Service, where we obtained thyroid function tests and thyroid ultrasound. The serum TSH concentration was 1.0 mIU/L (normal range 0.40 to 4.5), serum free T4 was 1.1 ng/dL (normal range 0.8 to 1.8), serum T3 was 113 ng/dL (normal range 76 to 181), thyroglobulin (Tg) antibodies <20 IU/mL (negative), and serum Tg level of 91 ng/mL (normal range 2.0 to 35.0). The neck sonogram revealed multiple bilateral thyroid nodules, varying from 0.6 to 1.3 cm, as well as multiple bilateral lymph nodes. The nodules were either mixed cystic-solid or hypoechoic, without any additional suspicious features. Fine-needle aspiration of two nodules was nondiagnostic, and a right neck lymph

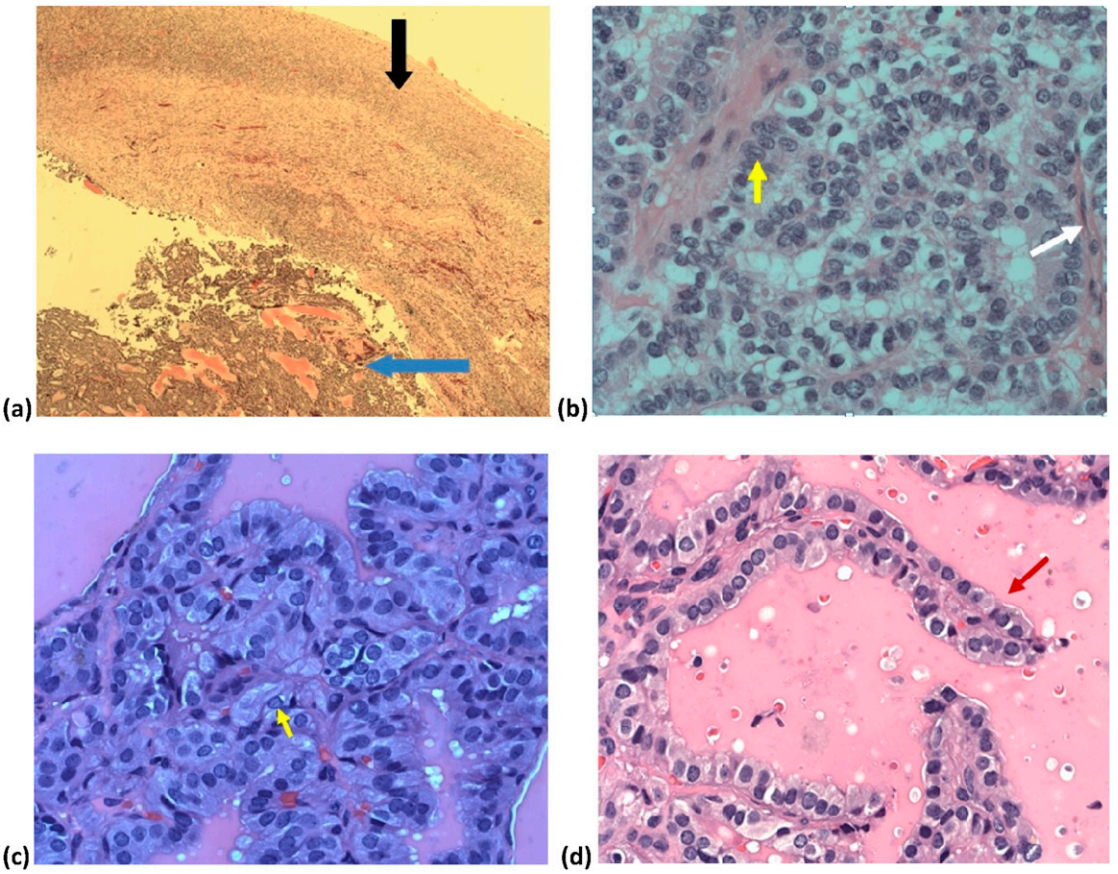

Figure 1. Hematoxylin and eosin staining of ovary and thyroid tumors. (a) Low-power magnification (×40) showing struma ovarii with PTC in ovary. Normal ovarian tissue is shown in top right field (black arrow). Struma ovarii is bottom right field (blue arrow). (b) PTC in struma ovarii (×400). There is papillary architecture with fibrovascular cores (white arrow). The tumor cells show nuclear enlargement, hyperchromasia, and numerous nuclear grooves (yellow arrow). This tumor harbored an *NRAS* Q61R mutation. (c) Classic PTC in thyroidectomy specimen (×400). This tumor also shows papillary architecture, nuclear enlargement, hyperchromasia, and nuclear grooves (yellow arrow). This tumor harbored an *HRAS* Q61R mutation. (d) PTC in thyroidectomy specimen (×400) demonstrating papillae (red arrow).

node fine-needle aspiration was compatible with CLL/SLL. Two months after the pelvic surgery, a total thyroidectomy was performed, and a small nodule (0.8 cm) in the left lobe was diagnosed as classical PTC [Fig. 1(c) and 1(d)]. The tumor was unifocal, without lymphovascular invasion, and no extrathyroidal extension was identified. The patient denied previous exposure to radiation, as well as familial history of thyroid cancer. After consideration of her entire clinical context, she had a recombinant human TSH–stimulated ^{123}I scan that showed only residual thyroid bed uptake with a stimulated serum Tg of 1.4 ng/mL. The patient had dosimetry and received 147.7 mCi of ^{131}I therapy, with only thyroid bed uptake and no evidence of distant metastasis on the post therapy scan. After 5 years of follow-up, the patient has no evidence of recurrent thyroid carcinoma: serum Tg level is 0.1 ng/mL, and neck sonogram and CT scan of the abdomen and pelvis demonstrate prominent lymph nodes, stable in comparison with previous exams, most likely related to her diagnosis of CLL/SLL.

Informed consent was obtained from the patient to perform molecular analysis of the tumors. The protocol was approved by the local institutional review board.

Molecular analysis of tissues obtained from both the malignant struma ovarii and the thyroid gland was performed using ThyroSeq v2. This panel can sequence and detect >1000 hotspots of 14 thyroid carcinoma-related genes, 42 types of gene fusions that occur in thyroid carcinoma, and mRNA expression level of 14 genes [5]. The same method was used to analyze tissue from a neck lymph node involved by CLL/SLL that was removed during the thyroidectomy.

Two different *RAS* mutations were identified in the PTC located in the thyroid and ovarian tissues. The thyroid gland tumor showed an *HRAS* Q61R mutation at 38% mutant allele frequency, whereas the PTC in struma ovarii harbored an *NRAS* Q61R mutation at 50% mutant allele frequency. No mutations were found in the adjacent normal ovarian tissue. No other mutations or gene fusions were identified. Additionally, both tumors had high levels of expression of the Tg, keratin-7, and *NIS* gene mRNA as typically seen in well-differentiated thyroid cells and carcinoma.

The molecular analysis of the neck lymph node was negative for *RAS* or other mutations.

2. Discussion

This report describes the rare occurrence of two different *RAS* mutations in PTC from struma ovarii and the thyroid gland: *HRAS* Q61R in the thyroid and *NRAS* Q61R in the struma ovarii. The finding of two different mutations provides evidence that these are two unrelated primary tumors, rather than metastasis from one site to the other.

The occurrence of malignant struma ovarii is rare. In a retrospective study over 25 years, out of 96 cases diagnosed as struma ovarii, Wei *et al.* [6] identified 10 cases of PTC, including eight cases of follicular-variant PTC and two cases of classic PTC. In that study, two cases of thyroid PTC with ovarian metastases were found. This diagnosis (*i.e.*, PTC originating in the thyroid gland and metastasizing to the ovary) implies the identification of thyroid gland primary carcinoma and the absence of thyroid tissue and a teratomatous component in the involved ovary [6]. In another study, out of 106 cases of struma ovarii over a 10-year period, Tan *et al.* [4] found only three cases of malignant struma ovarii, all of which were PTCs. One of the patients had a novel *BRAF* mutation (G469A), and a separate patient had a *KRAS* mutation (Q61R) in malignant struma ovarii; in a third patient, no mutation was found [4]. Other authors have identified different somatic mutations in malignant struma ovarii, mainly in *BRAF* and *RAS*, as well as *RET/PTC* rearrangement [7, 8].

This patient was found to have mutations at hotspot codon 61 in different genes: *HRAS* and *NRAS*. The 50% mutant allele frequency in the carcinoma from struma ovarii initially suggested that the mutation could also present in adjacent ovarian tissue, including stromal cells. To test this hypothesis, we performed molecular analysis of normal ovarian tissue, but no mutations were found in ovarian stromal cells.

Compared with other malignancies, there is a higher prevalence of *NRAS* mutations over *HRAS* and *KRAS* (8%, 3%, and 3%, respectively) in thyroid carcinoma [9]. Ninety-nine

percent of all *RAS* mutations occur at codons 12, 13, and 61. RAS mutants are unable to hydrolyze GTP into GDP, which is required to switch off the signal of activation [9]. Therefore, they are constitutively activated to a mitogenic (RAF/mitogen-activated protein kinase kinase/ERK cascade) and cell-survival pathway (phosphatidylinositol 3-kinase signaling cascade). Point mutations in one of the three *RAS* genes are found in ~13% of PTCs [10, 11]. Typically, tumors that harbor *RAS* mutations grow forming neoplastic follicles and are diagnosed as the follicular variant of PTC, but this was not the pattern observed in our patient. Importantly, activating point mutations of *BRAF* and *RAS* represent a dominant mechanism of PTC not related to radiation exposure [12]. The mechanism of *RAS* point mutation is not completely understood, but the fact that the patient had point mutations in different *RAS* genes suggests a similar mechanism of carcinogenesis in thyroid tissue at different locations.

The optimal surgical and postoperative treatment of patients with malignant struma ovarii is still controversial. Given the rarity of this condition, most of the knowledge is derived from case reports or small series of cases [2–4, 13]. Marti *et al.* [2] published a series of four patients and reviewed 53 reported cases to recommend the surgical management of well-differentiated thyroid carcinoma arising in struma ovarii. The authors suggest that pelvic surgery alone may be sufficient initial therapy and that prophylactic total thyroidectomy with radioactive iodine should be reserved for patients with gross extraovarian spread or distant metastasis.

Three large series of malignant struma ovarii have been published. In 1993, Devaney *et al.* [14] reviewed 54 cases of struma ovarii to define the histologic features that led to the diagnosis of malignant struma ovarii. They found that only 13 cases were malignant using thyroid gland criteria. Other authors analyzed 86 cases of malignant struma ovarii, including 26 in which the tumor had spread onto the surface of the ovary or beyond. They aimed to determine whether specific histologic features had predictive value in the clinical outcome of struma ovarii, but no correlation was found [15]. More recently, Goffredo *et al.* [16] used the Surveillance, Epidemiology, and End Results database to analyze a cohort of 68 patients diagnosed with malignant struma ovarii from 1973 to 2011. Their aim was to examine the survival rate of women diagnosed with malignant struma ovarii and to describe demographic, clinical, pathologic, and treatment characteristics of this population. In this series, 6 out of 68 patients had a concomitant diagnosis of thyroid carcinoma, representing a considerable excess of thyroid malignancies compared with the standard US population. This finding probably represents surveillance bias due to screening neck ultrasound or incidentalomas found during subsequent thyroidectomies. The overall survival rates at 5, 10, and 20 years were 96.7%, 94.3%, and 84.9%, respectively, regardless of the specific treatment used [16].

We believe that factors such as age, desire to preserve fertility of the patient, size of the ovarian tumor, presence of thyroid nodules, and need for radioiodine therapy should be taken into consideration for each patient. Considering the potential to metastasize over the years even when apparently restricted to the ovary, we advise prophylactic thyroidectomy and radioiodine as part of the management of malignant struma ovarii. This approach may contribute to the eventual finding of occult thyroid carcinomas, but it allows an adequate follow-up with serum Tg levels and imaging studies of the neck (sonogram) and pelvis (CT or MRI).

In conclusion, the finding of distinct types of *RAS* point mutation in thyroid carcinomas at two different locations provides definitive evidence that these carcinomas are synchronously developed independent primary tumors. However, because each of the carcinomas is driven by a *RAS* point mutation, it suggests a similar mechanism of carcinogenesis developing in thyroid tissue present in the same patient at the orthotopic and ectopic locations.

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