

THYROID CANCER TUMOR BOARD

Discordant Cytopathological Diagnosis of Well-Differentiated Thyroid Cancer Affects Patient Treatment

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CASE SUMMARY

A teenage girl had been diagnosed with Hashimoto's thyroiditis and a thyroid nodule about 2 years ago. She has a family history of autoimmune thyroid disease, and a grandmother also had a goiter. Her thyroid function was normal on presentation. A neck ultrasound revealed a 3-cm nodule. Fine-needle aspiration under ultrasound guidance was performed and cytology was consistent with follicular lesion of undetermined significance (FLUS). She sought several opinions for management of this nodule, and ultimately a decision was made to monitor it. Nine months later, a repeat ultrasound demonstrated growth of the nodule that then measured 4 cm in maximum dimension (Figure 1). A repeat biopsy with molecular

testing revealed follicular neoplasm, benign. Affirma gene expression classifier and negative MiRInform molecular panel. Because of the increase in nodule size and indeterminate cytology, a hemithyroidectomy was performed. Surgical pathology demonstrated a 4.5-cm minimally invasive follicular thyroid carcinoma (FTC) with a focus of vascular invasion. The margins were free of tumor. Also noted were foci of cellular architectural atypia, including insular and/or solid patterns.

A young patient with minimally invasive FTC typically has an excellent prognosis, but the focus of vascular invasion and insular components suggest a more aggressive tumor. The family requested a second review of the pathology, which was sent to an international expert. The second reviewer agreed with the assessment, reporting "We are dealing with a carcinoma of follicular cells which exhibits both capsular and vascular invasion. The latter is rather impressive in the sense of involving a large vessel located well outside the capsule of the tumor and attached to the wall of the vessel. There is also evidence of capsular invasion in adjacent areas." He continues, "the other important point relates to a focal insular pattern of growth, focal mitotic activity, and necrosis. I believe that these features are those of a poorly differentiated carcinoma focally developed within a better-differentiated lesion. My diagnosis therefore is follicular carcinoma with capsular and vascular invasion and poorly differentiated foci. This tumor is likely to follow an aggressive clinical course."

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Figure 1. Transverse view of right thyroid nodule that measures 1.8 by 1.9 by 4 cm. The nodule is well circumscribed and has a heterogeneous echotexture, without evidence of suspicious ultrasound features such as microcalcifications or internal vascularity.

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The patient underwent a completion thyroidectomy; there was no thyroid cancer in the contralateral lobe. Her family sought multiple opinions as to whether she should have postoperative treatment with radioactive iodine (RAI). Recommendations ranged from treating with 100 mCi to treating with 50 mCi to no RAI treatment (hormone suppression

alone). After much discussion about the risks and benefits of ^{131}I , the family opted for the 100-mCi dose. Just before the treatment, the patient sought another opinion; during slide review, the pathological diagnosis changed to encapsulated FVPTC [follicular variant papillary thyroid carcinoma] without capsular involvement.

ANALYSIS AND DISCUSSION

The discrepancy between opinions in the interpretation and diagnosis of surgical pathology for thyroid cancer among intrainstitutional reviewers and interinstitutional reviewers has been well documented in the literature, with rates of discordance of up to 83%. Notably, this can have a significant impact on the treatment of the patient (1, 2). In one retrospective review of 66 thyroid cancer cases by pathologists at the Institute of Pathology at Leeds, there was an 18% discrepancy in the diagnosis of 66 thyroid cases diagnosed between January 2001 and March 2003 (1). The changed diagnoses altered treatment in 5 of 12 patients and altered prognosis in all 12.

An area of particular difficulty is the diagnosis of follicular thyroid adenoma (FA), follicular thyroid carcinoma (FTC) and the follicular variant of PTC (FV-PTC) (1, 3). FTCs are divided into two major categories based on the degree of invasiveness: minimally invasive FTC and widely invasive FTC. The differential diagnosis of minimally invasive FTC includes FV-PTC, the most common subset of

papillary carcinoma, found in up to 56% of patients, depending on the geographic area (4, 5). FV-PTC is almost exclusively arranged in follicles lined by cells with characteristic papillary carcinoma nuclei. Furthermore, there are two categories of FV-PTC, encapsulated and invasive. Nuclear features encountered in follicular nodules often show some, but not all, of the nuclear features of PTC, making a clear-cut diagnosis of minimally invasive FTC or FV-PTC difficult. (3). A Mayo Clinic study in which 10 expert pathologists reviewed 87 cases initially diagnosed as FV-PTC ($n = 84$), FA ($n = 2$), and FTC ($n = 1$) demonstrated observer variability. There was 39% concordance from 10 expert pathologists after review of the same slides; concordance improved to 66.7% for cases with metastatic disease (6).

In addition to a similar invasive pattern (or lack thereof), encapsulated FV-PTC and minimally invasive FTC have other similarities. They rarely metastasize to lymph nodes (only 5% of cases), and the molecular profile is similar (Table 1). Encapsu-

Table 1. Histologic, Clinical and Molecular Profile of Encapsulated FV-PTC and Invasive FV-PTC.

Characteristic	Encapsulated FV-PTC	Nonencapsulated/Invasive FV-PTC
Invasiveness	Absent	Present
Lymph-node metastases	Rare	Common
Molecular testing	RAS, PAX8PPAR γ	BRAF, RAS, RET/PTC
Overall genotype and phenotype most similar to:	FA/FTC	PTC

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lated FV is close to the follicular carcinoma group of tumors, with a high prevalence of RAS mutation and very low BRAF mutation rate. Of 47 cases (28 encapsulated FV and 19 infiltrative FV) retrospectively reviewed at Memorial Sloan-Kettering from 1980 to 2002, a total of 11 of the 28 encapsulated FV had a mutation (10 RAS and 1 PAX8PPAR γ) and 9 of 19 of the infiltrative FV group harbored a mutation (5 BRAF, 2 RAS, 2 RET/PTC) (7, 8). While molecular genotyping can better classify these tumors into clinically relevant entities, morphologic examination and interpretation remains the final determinant of categorization in a majority of cases.

Liu et al. at Memorial Sloan-Kettering reviewed prognoses for FV-PTC in a series of 78 patients between 1980 and 1995 (9). Sixty-one patients had encapsulated FV and 17 had nonencapsulated FV. Patients with the encapsulated FV-PTC had the following characteristics: 98% negative margins, 5% lymph-node involvement, 5% extrathyroidal extension, 16% lymphovascular invasion, 14% capsular invasion, and no distant metastases. Over a median follow-up of 11 years, none of the 42 patients with noninvasive, encapsulated FV-PTC had recurrences or metastases or died of disease. These authors suggest that noninvasive, encapsulated FV-PTC should denote a benign clinical behavior and propose that patients with this variant may be treated with lobectomy (9).

While unanimity among diagnostic consultants is ideal, patients should know that a difference of opinion is quite common among experts. It does not mean that a mistake has been made, but undertreatment and overtreatment can occur, depending on the diagnosis.

Conclusions

The young patient described above had a growing mass with an indeterminate preoperative diagnosis and negative molecular panel. Postoperative surgical pathologic review by the local institution and an outside expert reviewer first suggested a potentially aggressive 4.5-cm follicular thyroid carcinoma with vascular and capsular invasion. A third review at a different institution revealed encapsulated, non-invasive FV-PTC, a diagnosis which has a benign clinical course. Many reports in the literature identify interobserver variability in pathologic interpretation particularly for follicular carcinomas and follicular variants of papillary thyroid cancer. Changes in clinical management occur in a significant percentage of cases depending on the pathology. Perhaps Next-Gen Sequencing (see Hershman review) will enable further diagnostic certainty preoperatively to assist in guiding management for these cases. Rather than the 100-mCi dose of ^{131}I recommended for FTC, our patient received 30 mCi of ^{131}I at the outside institution for FV-PTC. The posttreatment scan showed iodine uptake in the thyroid bed only, consistent with residual thyroid tissue.

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