

PATIENT HISTORY:

CHIEF COMPLAINT/ PRE-OP/ POST-OP DIAGNOSIS: Metastatic thyroid cancer.

PROCEDURE: Total thyroidectomy, excision lymph node.

SPECIFIC CLINICAL QUESTION: Not answered.

OUTSIDE TISSUE DIAGNOSIS: Not answered.

PRIOR MALIGNANCY: Not answered.

CHEMORADIATION THERAPY: Not answered.

ORGAN TRANSPLANT: Not answered.

IMMUNOSUPPRESSION: Not answered.

OTHER DISEASES: Not answered.

UID: C93FF278-A750-4487-8A22-7AC06BDFB799
TCGA-BJ-A022-01A-PR

Redacted

1C8-0-3
carcinoma, follicular, NOS 8330/3
Site: thyroid, NOS C73.9
lw 11/22/11**ADDENDA:****Addendum****Molecular Anatomic Pathology Testing:****Block 1D:**

- A. **HRAS** codon 61 mutation IDENTIFIED.
B. Mutations in **BRAF**, **NRAS61**, and **KRAS12/13** NOT identified.

Note:

DNA was extracted in the amount sufficient for testing.

Mutations in either **BRAF** or **RAS** genes or **RET/PTC** rearrangements are found in more than 70% of papillary thyroid carcinomas (1). **BRAF V600E** mutation has been associated with more aggressive behavior of papillary carcinoma (2, 3). The association between **BRAF V600E** mutation and features of tumor aggressiveness have also been observed in papillary microcarcinomas (4). Mutations in the **RAS** genes or **PAX8/PPARG** rearrangement occur in ~70% of follicular thyroid carcinomas and with lower frequency in oncocytic (Hürthle cell) carcinomas (5). Regarding the specificity of these mutations for cancer, **BRAF V600E** mutation and **RET/PTC** and **PAX8/PPARG** rearrangements are overall specific for malignancy in the thyroid, although they have been reported with a very low frequency in benign thyroid lesions (6). **RAS** mutations occur in malignant and benign thyroid tumors, being found in ~40-50% of follicular and anaplastic carcinomas, 30-40% of follicular adenomas and 10-15% of papillary carcinomas (6).

- Adeniran AJ, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. *Am J Surg Pathol* 2006, 30:216-222.
- Xing M, et al. **BRAF** mutation predicts a poorer clinical prognosis for papillary thyroid cancer. *J Clin Endocrinol Metab* 2005, 90:6373-6379.
- Elisei R, et al. **BRAF V600E** mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. *J Clin Endocrinol Metab* 2008, 93:3943-3949.
- Lee X, Gao M, Ji Y, Yu Y, Feng Y, Li Y, Zhang Y, Cheng W, Zhao W. Analysis of differential **BRAF(V600E)** mutational status in high aggressive papillary thyroid microcarcinoma. *Ann Surg Oncol*. 2009 Feb;16(2):240-5.
- Nikiforova MN, et al. **RAS** point mutations and **PAX8-PPARγ** rearrangement in thyroid tumors: Evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab* 2003, 88: 2318-26.
- Nikiforov YE. Recent developments in the molecular biology of the thyroid. In: Lloyd RV., ed. *Endocrine Pathology: Differential Diagnosis and Molecular Advances*. Humana Press, Totowa, 2004, 191-209.

Sample Preparation and Procedure

For paraffin-embedded surgical specimens, manual microdissection was performed to collect tumor tissue. Specimens with the minimum of 50% of tumor cells in a microdissection target are accepted for the analysis. Optical density readings were obtained. Real-time PCR was performed on the *LightCycler 480* to amplify **BRAF**, **NRAS** codon 61, **HRAS** codon 61, and **KRAS** codons 12/13 sequences. Post-PCR melting curve analysis was used to detect possible mutations. If required, the mutation type was confirmed by Sanger sequencing of the PCR product on DNA from samples positive for each of these mutations was used as positive controls. Amplification at 35 cycles or earlier was considered sufficient for the analysis. The limit of detection is approximately 10% of alleles with mutation present in the background of normal DNA and RNA.

Notified

Processed and passed before final path report review.
lw 11/22/11

Criteria	Yes	No
Diagnosis Discrepancy		
Primary Tumor Site Discrepancy	X	
stPAA Discrepancy		
Prior Malignancy History		
Case is (circle):		
Reviewer Initials	lw	
Date Reviewed	11/22/11	

Notifiable

Addendum

Molecular Anatomic Pathology Testing:

Block D:

- A. Loss of heterozygosity is IDENTIFIED at chromosome 22q.
- B. Fractional Allelic Loss is 9% (1 locus with loss / 11 informative loci).
- C. LOH at the VHL gene locus (3p.26) is NOT identified.

Note:

Loss of tumor suppressor gene alleles is known to occur in thyroid follicular neoplasias and to correlate with tumor progression. As reported in the literature, widely invasive carcinomas and anaplastic carcinomas frequently have a mean fractional allele loss of ~50% (1). Adenomas typically have lower frequency of LOH, frequently fewer than 10%. Minimally invasive and angioinvasive follicular carcinomas typically have intermediate results (1,2). Some studies have shown that LOH at the VHL gene locus is specific for malignancy and is associated with poor prognosis (2,3). However, not all tumors reveal such a correlation and, therefore, the LOH profile should be interpreted in the context of the cytologic and histologic findings and the patient's clinical history.

Sample Preparation and LOH Analysis

For cytology samples, extraction of DNA was performed from the fluid or sample provided. For surgical specimens, manual microdissection was performed to include neoplastic tissue and normal adjacent tissue. Specimens with the minimum of 50% of tumor cells in a microdissection target are accepted for the analysis. DNA was isolated using standard laboratory procedure. Optical density readings were obtained.

Fourteen microsatellite markers (listed below) that have been previously found to be involved in thyroid neoplasia and co-localize with known tumor suppressor genes were used for analysis. PCR was performed using fluorescently labeled primers and the products of amplification were detected using capillary electrophoresis on ABI3730 platform. Relative fluorescence was determined for individual alleles and the ratio of peaks was calculated (GeneMapper ABI 3730). Normal tissue was examined to determine whether the patient is heterozygous at the marker (genetically informative) and neoplastic tissue was then analyzed to detect loss of heterozygosity. Thresholds for significant allelic imbalance were determined using normal (non-neoplastic) specimens for every marker. Loss of heterozygosity was determined using $(N^+ / N^S) / (T^+ / T^S)$ formula and reported when allelic ratio for a particular marker was below 0.5 or above 2.0. When normal tissue was not available, peak height ratios falling outside of 2 SDs beyond the mean for each polymorphic allele pairing were assessed as showing loss of heterozygosity.

D1S1161	1p	1p35.1
D1S407	1p	1p36.21
D3S1038	VHL	3P25.3
D3S1539	VHL	3p26.3
D5S659	APC	5q23.2
D5S1384	APC	5q23.3
D9S251	CDKN2/p16	9p21.3
D9S1748	CDKN2/p16	9p22.2
D10S1171	PTEN	10q23.31
D10S1173	PTEN	10q23.31
D17S1844	p53	17p13.1
D17S786	p53	17p13.1
D22S1150	NF2	22q12.2
D22S268	NF2	22q12.2

References

1. Hunt JL, et. al. Molecular evidence of anaplastic transformation in coexisting well-differentiated and anaplastic carcinomas of the thyroid. *American Journal of Surgical Pathology* 2003;27:1559-64.
2. Hunt JL, et. al. A novel microdissection and genotyping of follicular-derived thyroid tumors to predict aggressiveness. *Human Pathology* 2003;34:375-80.
3. Hunt JL, et. al. Loss of heterozygosity of the VHL gene identifies malignancy and predicts death in follicular thyroid tumors. *Surgery*. 2003 Dec;134(6):1043-7; discussion 1047-8. 2003;134:1043-7.

FINAL DIAGNOSIS:

THYROID GLAND, TOTAL THYROIDECTOMY (42.5 GRAMS) –

- A. ANGIOINVASIVE FOLLICULAR CARCINOMA (2.8 CM), IN THE LEFT LOBE.
- B. MULTIFOCAL CAPSULAR INVASION IS IDENTIFIED.
- C. TUMOR IS <0.1 CM FROM THE MARGIN.
- D. BACKGROUND THYROID WITH NODULAR HYPERPLASIA.
- E. pT2 NX M1 (right femur).

CASE SYNOPSIS:

SYNOPTIC DATA - PRIMARY THYROID TUMORS

SPECIMEN TYPE:	Total Thyroidectomy
TUMOR SITE:	Left Lobe ✓
TUMOR FOCALITY:	Unifocal ✓
TUMOR SIZE (largest nodule):	Greatest Dimension: 2.8 cm
HISTOLOGIC TYPE:	Other: Follicular carcinoma
PATHOLOGIC STAGING (pTNM):	pT2 pNX Number of regional lymph nodes examined: 0 Number of regional lymph nodes involved: 0 pM1 Site(s) of metastasis: Right femur
MARGINS:	Margin(s) involved by carcinoma
VENOUS/LYMPHATIC (LARGE/SMALL VESSEL) INVASION (V/L):	Present
ADDITIONAL PATHOLOGIC FINDINGS:	Other: Nodular thyroid hyperplasia