Genomic Landscape of FNAs Positive for Medullary Thyroid Cancer and Potential Impact on Systemic Therapy

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BACKGROUND

Systemic therapies targeting specific genomic aberrations in advanced MTC are available or under investigation. The Afirma Genomic Sequencing Classifier (GSC) uses RNA sequencing to assess FNA specimens from cytologically indeterminate thyroid nodules, which are also tested for specific molecular aberrations associated with thyroid cancer via a suite of highly accurate malignancy classifiers. The Afirma Xpression Atlas (XA) is an RNA sequencing-based add-on tool that reports expressed nucleotide variants and fusions across 51 cancer-associated genes (figure 3) when added to Afirma GSC and/or malignancy classifiers.

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer that can appear in any cytology category. Previously, the Afirma MTC classifier demonstrated 100% sensitivity and specificity among 21 FNA samples that included 22 MTCs. Herein, we report the prevalence and genomic landscape of MTC classifier-positive (MTC+) FNAs in the Veracyte Clinical Laboratory.

METHODS

All Afirma GSC and malignancy classifier tests run in the Veracyte Clinical Laboratory between July 2017 and January 2019 were deidentified and examined for MTC+ cases. Afirma XA was run on all MTC+ cases and all variants and fusions were tabulated.

RESULTS

Examination of 29,895 FNAs revealed 90 MTC+ cases. Among consecutive Afirma GSC tests, 42 were Bethesda III (22.7%), 33 were Bethesda IV (0-50 out of 4,990; P=0.05), and 23 were Bethesda V (5-990). Provider-ordered Afirma testing was done on an additional 16 MTC classifier-positive (MTC+) cases from Bethesda V and VI nodules, respectively. Examining all MTC+ samples revealed that 58% harbored a RET variant (n=26), 9% contained a BRAF variant (n=5), 26% included no variant/fusion (figure 4). The most common were p.M918T (14) and p.C634R (11) variants. 1 had a BRAF/VEGFR2 variant and 1 had an additional HER2/ EGFR variant.

Malignant Nodules

Using RNA sequencing, Afirma Xpression Atlas reports expressed genomic variants and fusions among 90 MTC+ samples using the Afirma Xpression Atlas.

CONCLUSIONS

In our cohort of Bethesda III-VI MTC+ FNAs, the Afirma XA identified a variant or fusion in 74%. Currently approved or investigational therapies exist for cancers with RET, BRAF, HRAS, and/or malignancy classifiers. Among 90 MTC+ samples, 73% of our series might be eligible for treatment based on genomic information from FNA in advanced MTC, noninvasive FNA sample collection at the time of diagnosis may ultimately impact on targeted therapy selection.