EIF1AX mutation in a patient with follicular thyroid carcoma

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Abstract

Background The EIF1AX gene is a novel cancer gene that has previously found to be mutated in papillary thyroid carcinoma (PTC), follicular variant papillary thyroid carcinoma (FVPTC), and anaplastic thyroid carcinoma (ATC). We report a patient with follicular carcinoma found to have an EIF1AX mutation and discuss its role in tumorigenesis.
Patient Findings A 71-year-old woman presented with an enlarging right thyroid mass, which was follicular neoplasm on cytology. The fine needle aspirate of the nodule was examined with next generation sequencing (NGS) and found to harbor EIF1AX and TP53 mutations. The patient underwent right thyroid lobectomy with final pathology showing follicular carcinoma, oncocytic-Hürthle cell type with capsular and vascular invasion. The patient returned one month later for completion thyroidectomy with the left thyroid lobe found to be negative for malignancy.
Summary The EIF1AX gene encodes a protein that mediates protein translation. Mutations in the EIF1AX gene have previously been reported in the tumorigenesis of PTC, FVPTC, and ATC. We report an EIF1AX mutation in a patient found to have follicular carcinoma.
Conclusions This is a report of an EIF1AX mutation detected in a follicular carcinoma.

Introduction

It is becoming increasingly important for the thyroid surgeon to understand the current clinical application and future potential of molecular biology for the diagnosis, management, and prognostication of differentiated thyroid cancer. Diagnostic molecular markers such as BRAF, RAS, P53, and RET-PTC have facilitated the evaluation of thyroid nodules. Molecular testing may reduce the number of unnecessary thyroid procedures and completion thyroidectomies and may lead to a more individualized approach to thyroid surgery.

In their recent study of the genomic characterization of PTC, the Cancer Genome Atlas Research Network discovered many new driver mutations in PTC.[1] In a cohort of 496 PTC specimens, the EIF1AX gene mutation was identified as a novel driver gene in PTC tumorigenesis in six cases (1.2%). In the present case report, we describe the detection of a somatic EIF1AX mutation in a patient with follicular carcinoma, the second most common thyroid malignancy accounting for approximately 10-15% of all clinically evident thyroid malignancies.[2,3]

Patient

A 71-year-old female presented with an enlarging right thyroid mass. Despite increase in size of the mass on serial ultrasounds, the patient was reluctant to pursue surgery and opted to have NGS performed.

Ultrasound showed a 3.3 x 2.8 x 3.4 cm solid, heterogeneous, hypoechoic nodule. FNA was suspicious for a follicular neoplasm, Hürthle cell type. The NGS panel was positive for a c.338-1G>T splice site mutation in the EIF1AX gene. In addition, this FNA specimen was positive for a c.536A>G (NM-000546.5), p. H179R mutation in the TP53 gene. Given the association of EIF1AX as a driver gene in PTC, it was recommended that she undergo thyroid lobectomy.

The patient underwent uncomplicated right thyroid lobectomy. The final diagnosis was follicular carcinoma, oncocytic-Hürthle cell type, 3.5 cm in maximal dimension, with capsular and vascular invasion and no extrathyroidal extension identified.

One month later the patient underwent uncomplicated left completion thyroid lobectomy. Final pathology of the left thyroid lobe showed no evidence of malignancy. At one year follow-up the patient was doing well.

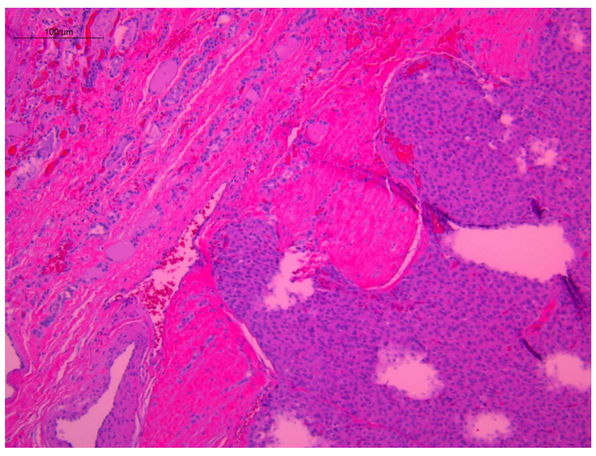
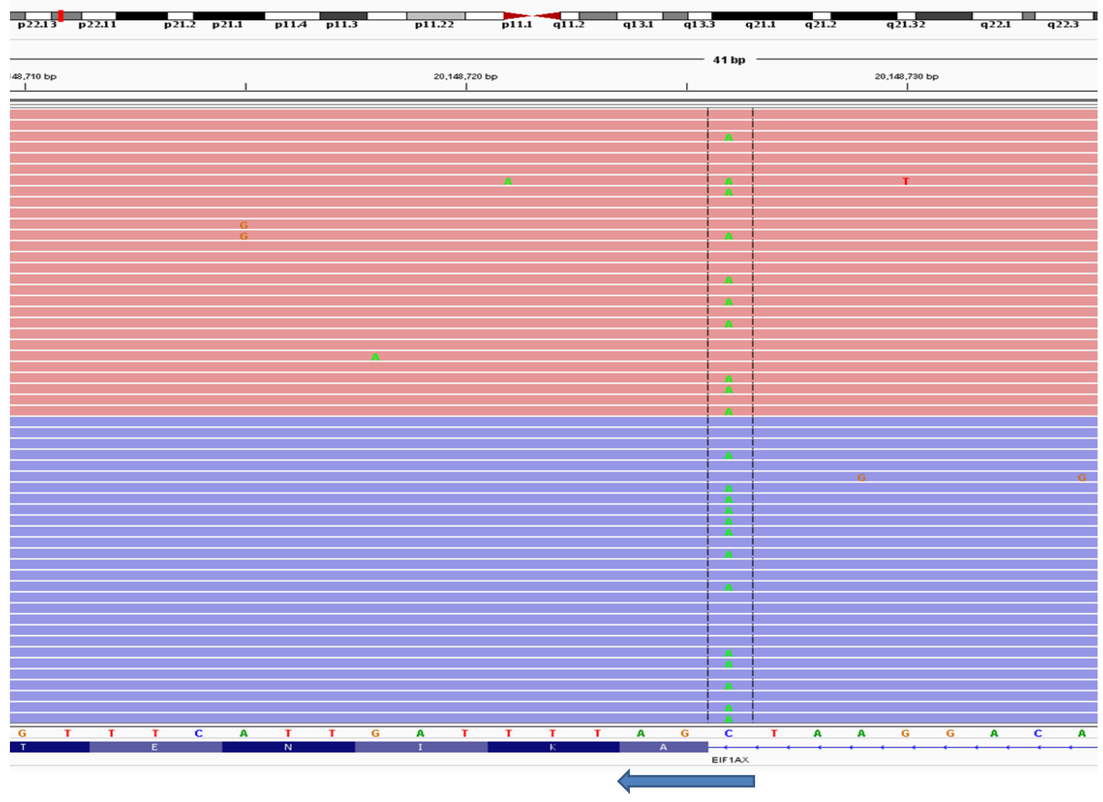


Figure I.
H&E stain. 20x magnification.
Slide demonstrates capsular invasion

Methods

FNA sample and FFPE tumor tissue were extracted for DNA with the QIAamp DNA Micro Kit/FFPE Tissue Kit respectively. DNA was sequenced by a custom NGS panel targeting 23 genes frequently mutated in thyroid cancer on MiSeq®system. The panel contained AKT1, APC, AXIN1, BRAF, CDKN2A, CTNNB1, DNMT3A, EGFR, EIF1AX, GNAS, HRAS, IDH1, KRAS, NDUFA13, NRAS, PIK3CA, PTEN, RET, SMAD4, TERT Promoter, TP53, TSHR and VHL genes, a total of 221 amplicons that covered full regions of tumor suppressor genes and hotspot regions of oncogenes. The Illumina VariantStudio software application was used to generate VCF files and all variants/mutations were interpreted by genomic analysts for their pathogenicity.



A113
Exon 6

Figure II. Identification of EIF1AX splice site mutation c.338-1G>T by MiSeq. Forward (Red) and reverse (blue) sequence reads are shown in IGV. The first amino acid of exon 6 (p.A113) and the direction of transcription is indicated by the arrow. EIF1AX is coded on the complement strand of the human reference genome strand. A nucleotide change of C to A on the reference strand shown in this image represents a G to T change for the EIF1AX c.338-1G>T mutation.

Discussion

To our knowledge, this is the first documented case of follicular carcinoma with an EIF1AX mutation. Karunamurthy et al analyzed 266 thyroid tumors and nodules and detected EIF1AX mutations in 2.3% of PTC.[4] Of the 53 follicular carcinomas analyzed, including 22 oncocytic Hurthle cell variants, 0 harbored EIF1AX mutations. EIF1AX mutations are more prevalent in Poorly Differentiated Thyroid Cancer (PDTC) and Anaplastic Thyroid Cancer (ATC).[5] Landa *et al.* found EIF1AX mutations in 11% of PDTC and 9% of ATC.[5] EIF1AX mutated PDTC showed significantly shorter survival and were present in larger tumors.[5]

EIF1AX mutations are clustered in two main regions, near the N-terminal domain in exon 2 or the unique splice acceptor site between exons 5 and 6 (A113_splice) where our patient's mutation occurred.[5]

The EIF1AX gene, encodes eIF1a, which is involved in the initiation of translation. eIF1a scans for the AUG start codon and mediates the transfer of 5' end of capped RNA to 40S ribosomal subunits, which forms the 40S pre-initiation complex. It is unclear how mutations in EIF1AX promote cancer, however it has been suggested that mutations in EIF1AX could decrease the rate of bulk translation.[6,7]

Conclusions

We present the first patient with follicular carcinoma found to have an EIF1AX mutation. The EIF1AX gene encodes a protein that is a key component of the translation pre-initiation complex. Mutations in the EIF1AX gene have previously been associated with PTC, FVPTC, and ATC and further studies are necessary to better understand its role in the tumorigenesis of thyroid carcinoma.

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