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EIF1AX Mutation in a Patient with Hürthle Cell Carcinoma

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Abstract The EIF1AX gene is a novel cancer gene that has been reported in the tumorigenesis of papillary thyroid carcinoma, follicular variant papillary thyroid carcinoma, and anaplastic thyroid carcinoma. A 71-year-old woman presented with a right thyroid mass, which was follicular neoplasm on cytology. The fine needle aspirate of the nodule was examined by next-generation sequencing and found to harbor EIF1AX and TP53 mutations. Right thyroid lobectomy was performed with final pathology showing Hürthle cell carcinoma with capsular and vascular invasion. We report an EIF1AX mutation in a patient found to have Hürthle cell carcinoma.

Keywords EIF1AX · Hürthle cell carcinoma · FNA · Thyroid · TP53

Case History

A 71-year-old female presented with an enlarging right thyroid mass. Ultrasonagraphy showed a 3.3 × 2.8 × 3.4 cm solid, heterogeneous, hypoechoic nodule of the right thyroid lobe. Fine needle aspiration (FNA) cytology was suspicious for a follicular neoplasm, Hürthle cell type. The FNA specimen was sequenced using a next-generation sequencing (NGS) thyroid panel that contains 24 commonly mutated genes for different subtypes of thyroid cancer. The FNA specimen was found to harbor a c.338-1G>T splice site mutation, commonly designated A113 splice mutation, in the eukaryotic translation initiation factor 1A, X-linked (EIF1AX) gene close to the C terminus of the encoded protein. This exact nucleotide position, c.338–1 G, with a G to C mutation was in one of the EIF1AX-mutated samples in the Cancer Genome Atlas Research Network dataset [1]. 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 papillary thyroid carcinoma (PTC), it was recommended that she undergo right thyroid lobectomy.

What Is Your Diagnosis? Figs. 1 and 2

Clinicopathological Diagnosis: Hürthle cell carcinoma.

The final pathologic diagnosis was Hürthle cell carcinoma, 3.5 cm in maximal dimension, with three foci of capsular invasion (Fig. 1) and one focus of vascular invasion (Fig. 2) and no extrathyroidal extension identified. Genomic analysis of this surgical specimen confirmed the previous cytological analysis showing a c.338-1G>T nucleotide change in the EIF1AX gene as well as the TP53 mutation. The patient subsequently underwent a left completion thyroid lobectomy. Final pathology showed no evidence of malignancy. Genomic analysis of the left lobe by the NGS thyroid panel showed no mutations of known pathologic significance. At 1 year follow-up, the patient was free of disease.

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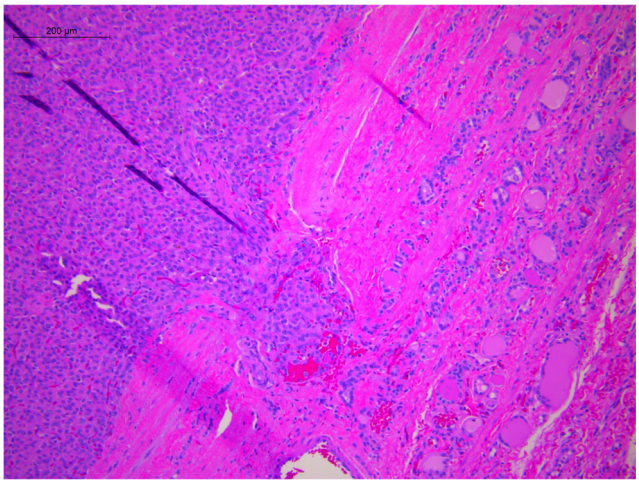

Fig. 1 Hürthle cell carcinoma with capsular invasion at low power

Comment

This represents the first reported case of Hürthle cell carcinoma (HCC) with an EIF1AX mutation. EIF1AX has recently been identified as a novel cancer driver gene in PTC by the Cancer Genome Atlas Research Network [1]. Their analysis of the genetic landscape of PTC identified EIF1AX mutations in five tumors (1.2%) lacking other known driver mutations as well as one EIF1AX splice site mutation [1]. The reported EIF1AX splice site mutation occurred at the identical nucleotide position as the present case, in a tumor having additional known activating mutations in both the KRAS and BRAF genes [1].

The NGS panel used to sequence the above-mentioned specimens uses a TruSeq custom amplicon panel designed to detect somatic mutations in 24 thyroid cancer-related genes (*AKT1*, *APC*, *AXIN1*, *BRAF*, *CDKN2*A, *CTNNB1*, *DNMT3A*, *EGFR*, *EIF1AX*, *GNAS*, *HRAS*, *IDH1*, *KRAS*, *NDUFA13*, *NRAS*, *PIK3CA*, *PTEN*, *RET*, *SMAD4*, *TERT promoter*, *TG*, *TP53*, *TSHR*, *VHL)*. The panel covers the full-length coding sequence plus splice sites for tumor suppressors, and mutational hotspots for oncogenes. Base calling, mapping and variant annotation was performed using Illumina's suite. Variant filtering and interpretation was performed using an in-house informatics pipeline (ClinMut Reporter). Given that both the FNA specimen and the final surgical specimen with the HCC were found to harbor the same A113 splice site mutation and the benign left thyroid lobe showed no mutations on NGS, it was concluded that the EIF1AX A113 splice site mutation was genuine and it contributed to the pathogenesis of this HCC.

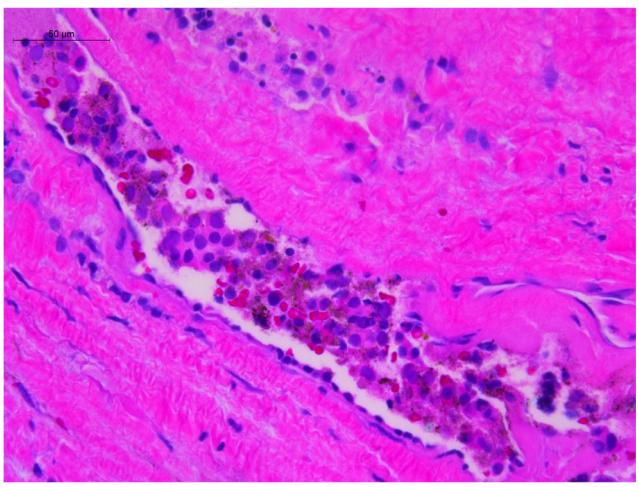

Fig. 2 Hürthle cell carcinoma with vascular invasion at high power

A recent study by Karunamurthy et al. detected EIF1AX mutations in PTC and anaplastic thyroid carcinoma (ATC), as well as benign nodules [2]. They analyzed 266 thyroid tumors and hyperplastic nodules and detected EIF1AX mutations in 2.3% of PTC. Of the 53 follicular carcinomas, including 22 oncocytic Hürthle cell variants, analyzed in their study, zero harbored EIF1AX mutations. The mutation was detected in 7% of follicular adenomas. 4.2% of FNA cytology samples with indeterminate cytology were found to have mutations in EIF1AX. Five EIF1AX mutation-positive FNA samples underwent surgery with one of five nodules being PTC. They concluded that EIF1AX mutations occur in both thyroid carcinomas and benign nodules and that mutations in EIF1AX confer an approximate 20% risk of cancer.

EIF1AX mutations are more prevalent in poorly differentiated thyroid cancers (PDTCs) and ATCs [3]. Landa et al. found EIF1AX mutations in 11% of PDTCs and 9% of ATCs [3]. In their study, of the 15 PDTCs and ATCs with EIF1AX mutations, 14 also harbored RAS mutations [3]. EIF1AX-mutated PDTCs showed significantly shorter survival and were present in larger tumors when compared to wild type EIF1AX PDTCs [3]. Another recent study examining whole-exome sequencing of 22 ATCs found EIF1AX mutations in three tumors (13.6%) [4]. No EIF1AX mutations were detected in any cases of ATC without a coexisting RAS mutation [4], while three of the six tumors with RAS mutations also harbored EIF1AX mutations [4]. Interestingly, our patient with HCC, a cancer with strong association with RAS mutations, was found to lack a RAS mutation.

Mutations in EIF1AX were initially discovered in uveal melanoma [5] and may be a poor prognostic indicator for metastasis in the disease [6]. These mutations are predicted to be late events in the progression of melanoma [6]. In addition, mutations in EIF1AX have also been associated with low-grade gliomas, lung adenocarcinoma, uterus endometrial carcinoma, ovarian cancer, and leptomeningeal melanotic neoplasms [7].

EIF1AX mutations are clustered in two main regions, near the N-terminal domain in exon 2 as seen in uveal melanomas or near the above mentioned unique splice acceptor site between exons 5 and 6 (A113_splice) where our patient's mutation occurred [3]. Functionally, these splice site acceptor site mutations result in a 12 amino acid deletion. More commonly, mutations in the EIF1AX gene occur at the A113_splice site, followed by a cluster of mutations in exon 2 [2]. Mutations at

the A113_splice site, particularly in combination with RAS mutations, are more commonly associated with thyroid cancer than isolated EIF1AX mutations or mutations at other sites [2].

The EIF1AX gene, located on chromosome X, encodes the eukaryotic translation initiation factor 1A (eIF1a), which is involved in the initiation phase 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 for protein translation. 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 [5, 8], because the gene encodes a protein that is necessary for the maximal rate of protein synthesis. Furthermore, overexpression of E1F1AX increases expression of Cyclin D1, a cell cycle regulator, triggering cell proliferation in vitro [9].

Our patient was also found to have a mutation in the TP53 gene. The TP53 gene is a tumor suppressor gene that regulates cell cycle and apoptosis and commonly coexists with other driver mutations. Inactivating mutations of the TP53 gene have been considered to be the hallmark of ATC, with mutations of TP53 being one of the genetic events distinguishing ATCs from PDTCs [10]. In our patient's case, the EIF1AX mutation was likely the driver mutation, which along with the mutation in TP53 resulted in tumorigenesis. The more aggressive behavior of our patient's tumor may have been due to the TP53 mutation.

In summary, we present the first patient with HCC of the thyroid found to have an EIF1AX mutation. The EIF1AX gene encodes a protein that is a key component of the translation pre-initiation complex. EIF1AX mutations are predictive of worse survival in PDTCs and have the potential for use in risk stratification and as a prognostic indicator in a heterogeneous disease. Mutations in the EIF1AX gene have previously been associated with PTC, FVPTC, ATC, and benign nodules, and further studies are necessary to better understand its role in the tumorigenesis of thyroid carcinoma.

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