AMP CONFERENCE
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#G043

THE IMPORTANCE OF PRECISION MEDICINE TO UNCOVER A PATIENT'S TRUE DIAGNOSIS

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PROTEAN BIODIAGNOSTICS

Background

Accurate diagnosis of cancer type is crucial to guide patients to a correct drug for therapy, prevent unnecessary procedures, and increase life expectancy. However, patients are frequently misdiagnosed, as evidenced by our case.

Objective

Here we present a case that was originally diagnosed with hepatocellular carcinoma and underwent immunohistochemistry (IHC) and genetic testing via Invitae and TSO500. This case was then referred for Protean MAPS™ (Protean BioDiagnostics) analysis.

Design/Methods

A male in his 50s was originally diagnosed with hepatocellular carcinoma. This case was referred for Protean MAPS™ (Protean BioDiagnostics) analysis, a diagnostic testing service including pathology review, comprehensive in-house molecular testing, and virtual molecular tumor boards. Patient results were further analyzed using SOPHIA DDM, a variant annotator which additionally identifies rare large-scale insertion or deletions (indel). Results were then compared to findings from the COSMIC and cBioPortal databases.

DIAGNOSTIC TESTS

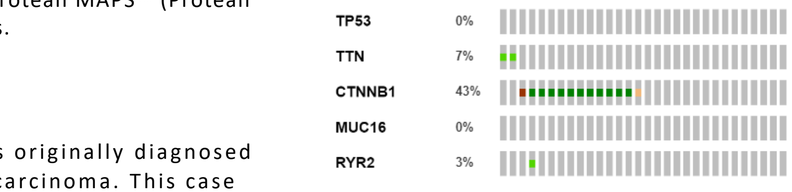
A. INVITAE germline testing

Invitae's diagnostic testing result via the Multi-Cancer Panel (84 genes)

Gene	Result	Classification
CDKN1B	c.274C>T	VUS
CEBPA	c.1021A>G	VUS
MSH3	c.2623G>A	VUS
MUTYH	c.56G>A	VUS

B. cBioPortal analysis

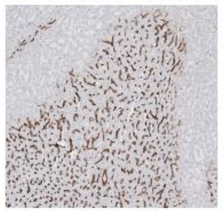
5 commonly altered genes in hepatocellular carcinoma were compared to adenoma samples in the OncoPrint below

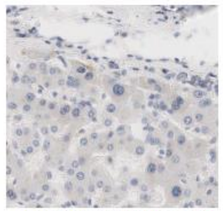


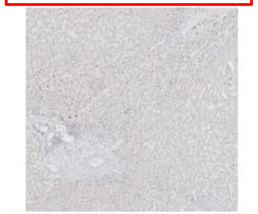
C. Immunohistochemistry

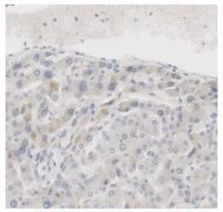
IHC done for patient comes back with strong expression of glutamine synthetase and other key negatives

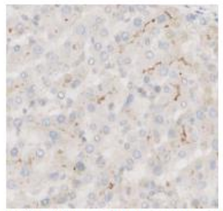

IHC glutamine synthetase- strong expression in adenoma


IHC CD34 in nodule


IHC ki67 no staining in nodule


IHC PDL1 SP263 negative no stain


IHC TP53 no evidence of stain


IHC p-CEA negative for expression

D. SOPHIA DDM

CAP/CLIA variant annotator using the TSO500 raw data (523 genes) as input

P	P...	★	⚠	T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
A	5	★		INDEL	CTNNB1	splice_donor_cds_indel	c.52_414del	2446	2.4	GACAG...	G
B	4			SNP	PIK3CA	missense	c.317G>T	1491	5.8	G	T
B	4			SNP	RAD52	nonsense	c.1245T>G	679	48.3	A	C
B				SNP	ANKRD11	missense	c.3812C>T	2404	49.4	G	A
B				SNP	AXIN1	missense	c.1205C>T	744	57.8	G	A
B				SNP	CDKN1B	missense	c.274C>T	2256	37.5	C	T

Results

Initial blood test and genetic testing results were unremarkable. SOPHIA DDM, however, reported a somatic catenin (CTNNB1 c.52_414del) deletion. This rare indel features deletion of exons 3 and 4 of CTNNB1. The exon 3 region contains proteasomes, important for β-catenin degradation, and the deletion causes a gain-of-function resulting in degradation-resistant β-catenin protein. Data compared to findings in the COSMIC database confirmed liver adenoma. The cBioPortal also confirmed liver adenoma, as CTNNB1 mutations without TP53, RYR2, and/or MUC16 alterations were more likely to be classified as adenomas. Out of three possible distinct adenomas, patient's results aligned with the benign β-catenin–mutated hepatocellular adenoma. This new diagnosis also supports the IHC result, where the stains depicted upregulated glutamine synthetase – a feature consistent with hepatic adenoma.

Conclusion

In our case, the patient was initially misdiagnosed with a liver cell carcinoma, which could have led to drastic life changes. A comprehensive review using SOPHIA DDM's use of rare INDEL detection, NGS sequencing providing key negatives, and the effectiveness of precision medicine assisted in the proper diagnosis of this patient.

References

- "Physicians Misdiagnose at an Alarming Rate." National Center for Policy Analysis. National Center for Policy Analysis, 08 May 2013. Web. 18 Nov 2013.
- Cerami et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discovery. May 2012 2; 401. PubMed.
- https://www.proteanbiodx.com/testingservices

Male
Age 50
Suspected Hepatocellular carcinoma

→ Liver Biopsy: IHC (Protean BioDiagnostics)

→ Liquid Biopsy & Invitae initial analysis

→ Next Generation Sequencing: TSO500

→ Variant annotation (SOPHIA DDM)

→ cBioPortal analysis and literature review

→ Updated diagnosis: Hepatocellular adenoma