AOT ANNALS OF THYROID
AN OPEN ACCESS JOURNAL PUBLISHING RESEARCH IN ALL ASPECTS OF THYROID DISEASE

Peer Review File

Article information: https://dx.doi.org/10.21037/aot-21-20

Reviewer Comments

Well-written case report of a clinically important topic. Illustrations support the main findings, and the discussion is for most parts balanced. There is no page numbering which makes specific references to the uploaded text version hard to pinpoint, but I will try to be as specific as possible. A few concerns:

1. The affiliations of the authors need clarifications, as two have affiliations to medical companies rather than academic institutions, but yet no disclosure is made in the disclaimer section? Please explain.
Reply: The authors have completed the COI forms and under the new disclaimer section in the text it will be disclosed that they are associated with for profit organizations.
Changes in the text: Added to the footnote "All authors have completed the ICJME disclosure form. The authors have no conflicts of interest to declare. Authors P.A. and J.M. do disclose that they are employed by a for-profit healthcare organizations." Page 10, Line 21-23.

Changes in the text #2: Added "[1]Rocky Vista University College of Osteopathic Medicine, Parker, CO, USA. [2]South Valley ENT and Steward Healthcare Inc., Salt Lake City, UT, USA. [3]Professional Diagnostics Inc. and Steward Healthcare., Salt Lake City, UT, USA.
Correspondence to: Jeffery Mohlman, M.D., M.P.H., Jordan Valley Medical Center, 3580 W 9000 S West Jordan, UT 84088 Telephone: 801-601-2337 Fax: 801-601-2674 Email: Jeffrey.s.mohlman@gmail.com" Page 1, Lines 3-7

2. Was patient consent for this report obtained?
Reply: Multiple attempts were made to contact the patient in order to obtain consent. However, the phone numbers listed for the patient are no longer working and no contact could be made. Unfortunately, consent was unable to be obtained.
Changes in the text: None.

3. The role of DICER1 in thyroid tumorigenesis should be expanded a bit in the Discussion or Intro sections, as this gene is not only responsible for many poorly diff

TCs arising in young patients, but also reported as recurrently mutated in FTCs, particularly of the macrofollicular type. Please revise and cite the relevant papers. Also, the statement "The DICER1 gene is vital in the control of gene expression" is too blunt, in fact, DICER1 is a miRNA processor gene with a master regulatory role in this aspect. Please revise and cite relevant papers.

Reply: Added additional information describing the function of the DICER and its role.

Changes in the text: Added "The DICER1 gene is responsible for encoding the DICER endoribonuclease protein that is important in the control of protein translation, specifically microRNAs (miRNAs). As a component of the RNA induced silencing complex (RISC), DICER's role is to transform the single stranded pre-microRNAs into double stranded RNAs that can then be transported and bind to specific mRNAs. The binding of the miRNA to the mRNA prevents the attachment of ribosomes and subsequently, any protein translation that would have followed [5,14]. It is thought that the absence of a functional DICER protein may contribute to either a loss of function in tumor suppressor genes, or a gain-of-function in oncogenic genes that are regulated by the presence of inhibitory miRNA. Defective, downregulated, or even over expression of miRNAs resulting from a DICER1 mutation may lead to the development of cancer, or a poor prognosis in cancer [15, 16, 17]." Page 8, Lines 14-23

3. There is a recent case published with a similar presentation but no DICER1 mutation (PMID: 34389035). The authors of that study found a germline MET gene mutation. Is the MET gene included in your panel? Please explain, and compare your findings.

Reply: The Met gene was included in the evaluated biomarkers in the NeoTYPE Discovery Profile for Solid Tumors from Neogenomics Laboratories and were negative for findings involving the Met gene.

Changes in the text: Added "The panel used tests for well over 100 biomarkers and resulted in pertinent negatives such as BRAF, BRCA1, BRCA2, EGFR, KIT, KRAS, NRAS, PDGFRA, PIK3CA, ALK FISH, MET FISH, PDGFRe FISH, PTEN FISH, RET FISH, and ROS1 FISH." Page 6, Lines 16-18

Changes in Text #2: Added "Notably, a recently published case of a metastatic poorly differentiated thyroid carcinoma arising from a papillary thyroid carcinoma in a 28-year-old patient had shown a germline MET mutation. The MET gene encodes a receptor tyrosine kinase, which in tandem with the MET ligand, Hepatocyte growth factor (HGF), stimulates the MET-HGF pathway

resulting in cellular proliferation, mitosis, apoptosis and motility [18,19]. Mutations in the well-known MET oncogene can also be found in a variety of cancers not unlike MYC gene amplifications and may play a role in their dedifferentiation. Our case was negative for any MET abnormalities." Page 9, Lines 5-11

4. Speaking of the panel used, is it used in clinical routine practice at the authors' home institution?

Reply: This panel is not used in routine clinical practice and was performed because it included the DICER1 gene. Author 3 attempted to find a more streamlined panel for the DICER1 gene in PDTC but this proved challenging and a more broad panel was selected.

Changes in the text: None.

5. The nomenclature used for the gene gains is not familiar to me, for example RET (>2F, 24.0%, negative <16.2%). Please explain this nomenclature or revise.

Reply: >2F refers to the presence of 2 or more fusions seen; 24% refers to greater than 2 fusions were scene in 24% of the cells counted; negative <16.2% refers to the negative cutoff where as long as the percent of abnormal cells is below 16.2% than the sample would be considered negative.

Changes in the text: Added "[Fusion cutoff, % of cells counted, Negative cutoff]" to help with interpretation. Page 7, line 3

6.Do all text passages (phrasing and wording) stem directly from the authors? To me, it seems like the path report is pasted directly into this document? If so, please indicate with quotation marks, or re-write.

Reply: Consultation pathology reports were used in reference for the write-up of the microscopic description, but no direct quotations were used. This holds true for the initial pathology report. The write-up is an original.

Changes in the text: None.