Author’s response to reviews

Title: Papillary thyroid carcinoma with pleomorphic tumor giant cells in a pregnant woman - a case report

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Author’s response to reviews:

Dr. James Mockridge
Editor-in-Chief, BMC Endocrine Disorders

Stockholm, April 5th 2018

Dear Dr. Mockridge,

Please find enclosed our revised Case Report entitled “Papillary thyroid carcinoma with pleomorphic tumor giant cells in a pregnant woman – a case report” (BEND-D-17-00251) by Johan O. Paulsson, Jan Zedenius and C. Christofer Juhlin.

We would like to thank you and the referee for considering our manuscript, as well as proposing changes which we feel greatly enhanced the quality of the original report. Changes to the manuscript are marked up in yellow in the main text body, and each specific response to the comments raised follow below. We also took the liberty to update the follow-up time of the patient, as she is still without biochemical evidence of recurrence.

Editorial comment

“Your manuscript "Papillary thyroid carcinoma with pleomorphic tumor giant cells in a pregnant woman - a case report" (BEND-D-17-00251) has been assessed by our reviewers. They have
raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Endocrine Disorders.”

Reply: We thank the Editor for this comment. All points raised have been clarified in the revised version of our report, and each specific answer is detailed below in a point by point manner.

Reviewer reports:

Naoki Oishi (Reviewer 1): This is a case report by Paulsson et al. describing a papillary thyroid carcinoma with pleomorphic tumor giant cells (PTC-GC) in a 28-year-old woman. Since PTC-GC seems to have more favorable outcome than PTC with minor anaplastic carcinoma component [such as PTC with spindle and giant cell carcinoma (PTC-SGC)], they tried to distinguish it conducting genetic testing for BRAF, TP53, and TERT.

Overall, this is a well-written paper; however there are some major and minor criticisms.

Major

1) Were the pleomorphic giant cells in the PTC identified on the preoperative cytology? If present, it is interesting and important to recognize the potential diagnostic pitfall to misdiagnose PTC-GC as anaplastic thyroid carcinoma (ATC). Therefore, authors should describe whether there pleomorphic giant cells were positive or negative in cytology.

Reply: We thank the reviewer for this thoughtful comment. The cytological report was consistent with papillary thyroid carcinoma (Bethesda VI), the tumor displayed classical PTC nuclear features, was positive for CK19 and HBME1. The FNA Ki-67-index was estimated as 3-5%. Pleomorphic giant cells were not reported. This information has now been added to the manuscript at lines 78-79.

2) Authors reported that the PTC-GC exhibited necrosis in its conventional PTC area. Is it real necrosis (due to high proliferation) or secondary necrosis after puncture of fine needle aspiration? Please provide a microscopic photograph if necessary.

Reply: This is a good point. After re-analyzing the original slides as well as the pathology report, we conclude that the small foci of necrosis observed across the tumoral landscape were indeed tumor-related – and since this phenomenon was multifocal and without other degenerative changes associated to FNA punction (fibrosis, calcifications) – the necrosis is therefore highly unlikely to be due to the FNA puncture. We have clarified this aspect in the manuscript (rows 102-104) and amended a photomicrograph of one such necrotic area in Figure 1.
We also removed the sentence (and associated reference) regarding the Memorial Sloan-Kettering criteria for poorly differentiated thyroid cancer, as the new WHO classification from 2017 adhere strictly to the Turin proposal, and instead we amended the 2017 WHO classification as a reference (rows 101-102).

3) Authors should discuss how these giant cells are developed in the PTC. Follicular adenomas (FAs) may exhibit focal pleomorphism with bizarre nuclei, which are largely considered to be degenerative changes, and such pleomorphic FAs are referred to as "FAs with bizarre nuclei" according to the new WHO classification. It would be better to discuss the similarity and difference between the pleomorphic cells seen in PTC-GC and FA with bizarre nuclei.

Reply: We agree with the referee that the similarities between these two entities should be properly discussed. We have therefore added a paragraph to the Discussion and Conclusions section in which this topic is covered (rows 221-226).

4) Authors reported that they diagnosed this case as PTC-GC largely depending on the results of molecular testing: absence of TP53 and TERT promoter mutation, since TP53 and TERT promoter mutations are shown to be associated with anaplastic transformation. However, even before conducting molecular analysis it is highly unlikely that TERT promoter mutation occurs in such a young patient, because TERT promoter mutation has strong association with older patient's age. Actually, there have been only few TERT-mutated PTCs reported in patients younger than 40 years old. Therefore, it is still obscure whether genetic testing for TERT promoter mutation is useful in such a young patient. The authors must discuss the association between patient's age and TERT promoter mutations before they stress the importance of genetic testing.

Reply: We agree that TERT promoter mutations in well-differentiated forms of thyroid cancer (PTC and FTC) are heavily coupled to older patient age. The reason for conducting this molecular analysis was to exclude an ATC component, as ATCs exhibit TERT promoter mutations in the vast majority of cases. Therefore, we believe a positive outcome (i.e. finding of a TERT promoter mutation) in such a young patient would strongly point towards a more aggressive form of the disease, and support a focal ATC component. We have added a passage of text discussing the relationship between age and TERT promoter mutations to the Discussion and Conclusions section (rows 189-197).
Minor

1) Although authors provided Ki67-labeling index (around 30%) in the pleomorphic area, they should also note the mitotic counts there.

Reply: We agree with the reviewer. The mitotic count was 5 mitoses/10 HPFs in the pleomorphic areas, and this piece of information has now been added to the Case Presentation section in row 109.

2) The word "proliferation counts" is confusing. Please clarify whether it means "high mitotic counts" or "high Ki67-labeling index" in each time.

Reply: We thank the referee for pointing this out. By “proliferation counts”, we mean "high Ki67-labeling index". We have now replaced the term “proliferation counts” with “Ki67-labeling index” across the main body text.

3) In background, "how different clinical, histological and immunohistochemical analyses was used" should be modified to "how different clinical, histological and immunohistochemical analyses were used".

Reply: We thank the referee for spotting this grammatical error. The sentence has been modified as suggested by the reviewer at row 67.

4) In Case Presentation, the level of thyroglobulin ("0.2") should be noted with appropriate unit.

Reply: The appropriate unit (micrograms per liter) has been amended to the Case Presentation section at row 160.

5) In Figure Legend "e", it should be clearly annotated that it is immunohistochemistry for Ki67.

Reply: The Figure Legend has been revised accordingly.

We again thank the referee for improving our manuscript substantially. We hope that the Editor and reviewer find the above suggested changes are in line with their intentions and will find our manuscript of sufficient quality to warrant publication.
Best regards,

Carl Christofer Juhlin, MD, Associate Professor

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