Author’s response to reviews

Title: Late onset asymptomatic Pancreatic Neuroendocrine tumor - A case report on the phenotypic expansion for MEN1

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Author’s response to reviews:

Dear Jan Lubinski,

We thank you for your review and comments. Please see below our responses to reviewer comments.

Responses are in italics.

Reviewers’ comments:

Reviewer #1: Primary hyperparathyroidism is the most common part of MEN1 which occurs in 95% of MEN1 patients. It means that many affected people do not develop mentioned MEN1 component. 5% cases without PHP is enough common not to pay special attention to publish this case report. I congratulate MEN1 investigation in your Genetic Department. Maybe you can present new mutations or undescribed MEN1 constellations.
Unclear if there is a question or comment to address here – The purpose of this article is to show the late phenotypic presentation and reminder that phenotypic variability exists

Reviewer #2: Kaiwar et al present an interesting case report with an important message.

I have a small number of comments that could be considered to improve the presentation.

1. I commend the authors for referring to "variants" in MEN1 -rather than using an array of confusing and ill-defined vocabulary that can be used in similar genetics papers. However, if the authors are associating these variants with disease susceptibility that should be stated. For example, at page 2 line 25-6 "About 10-20% patients with familial MEN1 do not have a detectable variant in the MEN1 gene". I assume "variants" in this instance is referring to variants that are known/predicted to be associated with disease risk? This should be clarified. Similar issue at page 2 line 33-4.

   Yes the reviewer is correct and makes a good point. We had qualified all mentions of ‘variant’ with ‘pathogenic variant’.

2. Page 3 Line 46. It is not clear to me what is meant by "variation in this residue". Are the authors referring to the amino acid or to the nucleotide? Could this be rephrased for clarity? Are these variants predicted to make any protein?

   Yes amino acid residue, we had added amino acid to clarify. Yes they do make some protein.

3. Please state the MEN1 genetic variant/s that is/are relevant to page 3 line 45, reference 9.

   This has been added (C.2T>A)

4. The word propositus and proband seem to be used interchangeably - perhaps proband is the more widely recognized and could be used throughout?

   All mentions of propositus have been replaced with proband

5. Does the last sentence mean to propose that once identified a person with MEN1 should be carefully screened for MEN1 related cancers OR that medical geneticists should carefully
screen people to enable the identification of people with MEN1 (or both) - this is not clear with the current sentence.

We have re-written this sentence for clarity and it now reads ‘The report signifies the importance of medical genetics consultation for diagnosis of MEN1, and, careful screening for MEN1 associated tumors when a pathogenic variant is identified.’

Very nice paper.
Thank you!

Reviewer #3: This is an interesting case report that adds to available informatin and phenotype of MEN1 Mutation carriers.

I would like to suggest to include a short Review on a possible association of EN1 with the mentioned lymphoma, that the Patient described was diagnosed with. There might be some evidence, that there is an association with the deleterious Mutation.


This is an interesting observation; we had added this reference and a short paragraph discussing it in the discussion. This paragraphs reads ‘Regarding the patient’s co-existence of MEN1 and lymphoma, there has been a prior case report [15] demonstrating this, and indeed it is an interesting observation. Whilst no known association or mechanism exists in the medical literature, to our knowledge this is only the second case of MEN1 and lymphoma in the same patient. This may be purely co-incidental however given the lack of other cases.’

Some minor typos.

Have gone over manuscript and checked for typos. Thank you.

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We have also moved the figure legends after the reference and thank you for pointing out an error/discrepancy in the author list. This has been corrected to the original author list when the manuscript was first submitted with no changes.