December 8, 2017

Ze-Mao Gong
Science Editor
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Dear Dr. Gong,

Enclosed please find our revised manuscript, "Hereditary Diffuse Gastric Cancer: One Family's Story." Thank you for your thorough and thoughtful review of our case report. We appreciate the overall positive comments of the reviewers. We have incorporated the suggestions of the reviewers, and believe that the resulting case report is significantly strengthened. We hope you will now find it acceptable for publication in *World Journal of Gastroenterology*.

We indicate in the response below how the reviewers' concerns have been addressed and where the changes can be found in the revised manuscript.

On behalf of all co-authors,

Keith Sultan

Reviewer #1: In the present study the authors are presenting a case with hereditary diffuse gastric cancer caused by a autosomal dominant genetic mutation in the CDH1 gene. Also they include data regarding patient's pedigree and genetic testing results of relatives. The manuscript is clearly presented and gives the background into the subject. The data are consistent, concordant and well presented. A minor observation: in introduction page 3, the word "mutation" is missing in the phrase: "the majority of HDGs are caused by an autosomal dominant inheritance of tumor suppressor gene CDH1."

Author Response:
Thank you for your positive review of our manuscript. We have edited the manuscript as follows to account for the error you have brought to our attention – "The majority of HDGCs are caused by an autosomal dominant inheritance of an abnormal copy of the tumor suppressor gene *CDH1"* (Page 4, lines 6-7).

Reviewer #2: The study demonstrates that the patient having CDH1 gene mutation has high risk for hereditary diffuse gastric cancer. In discussion, it is described that the patient in the study was fortunate to have the early detection. The reason for the early detection in spite of the low yield of random biopsies and the negative PET scan may be described more in detail.

Author Response:
We have included a more thorough discussion of the reason for our patient's early detection of gastric cancer (Page 8, lines 2-10). The detection of the patient's gastric cancer was early as it was detected when it was staged a T1, and therefore non-invasive. The 70-80% penetrance of the

CDH1 mutation coupled with the patient's diagnosis of gastric cancer 10 years prior and the death of 3 family members due to metastatic gastric carcinoma, suggest that the patient's cancer would have ultimately progressed if it had been left undetected. Our patient was thus highly fortunate that the random biopsy was taken in the correct spot to detect the gastric cancer, while all other biopsies taken were negative. We have also included a discussion of the timing of metastatic disease (Page 7, lines 14-19).

Review #3: "Hereditary Diffuse Gastric Cancer: One Family's Story", by Zylberberg et al. described the clinical courses of families suffering HDGC. In this manuscript, important information on the reported case and his family is concisely summarized, and manuscript itself is well written. As authors described, this case highlights the importance of gathering a thorough family history and encouraging genetic testing in patients who meet the IGCLC criteria.
I have only a few comments as following;

Minor

1. Testing method for detecting CDH1 mutation should be described. Were the samples DNA from patients' lymphocytes? Please show whether the sequencing method for the detection of the mutation was Sanger sequencing or Next-generation sequencing.

Author Response:
The sampled DNA was obtained from the patient's lymphocytes and next-generation sequencing was used. This has now been added to the case report (Page 5, lines 22-23).

2. If examined, are there any somatic mutations detected in the gastric cancer tissues? Is the only CDH1 mutation sufficient for gastric cancer initiation or progression?

Author Response:
Unfortunately, the gastric cancer tissue was not examined for the presence of any somatic mutations. This has been added to the case report (Page 5, lines 18-19). Because *CDH1* encodes for E-cadherin, a cell to cell adhesion protein which plays a significant role in cell structural integrity, absent expression of E-cadherin allows for abnormal maintenance of cell architecture. *CDH1* is a tumor suppressor gene with autosomal dominant inheritance and therefore is thought to follow the two-hit hypothesis; a somatic mutation in the second E-cadherin allele is needed in order to cause cancer progression. This has been shown to occur mostly through *CDH1* promoter hypermethylation, with some instances of loss of heterozygosity. One study found that no additional somatic mutations beyond promoter hypermethylation was required for cancer formation. This is now reflected in the case report (Page 7, lines 4-10).

3. In Figure 2, it would be better that magnification powers are described in every figures or figure legends.

Author Response:
We have now added the magnifications to Figure 2 (Page 16).