

January 15, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (**file name: 12625-case report.doc**).

Title: Glucagon receptor gene mutations with hyperglucagonemia but without the glucagonoma syndrome

Authors: Helen C Miller, Mark Kidd, Irvin M Modlin, Patrizia Cohen, Roberto Dina, Panagiotis Drymoussis, Panagiotis Vlavianos, Günter Klöppel, Andrea Frilling

Name of Journal: *World Journal of Gastrointestinal Surgery*

ESPS Manuscript NO: 12625

The manuscript has been improved according to the suggestions of reviewers:

1 The comments section has been added to the manuscript summarizing the Case characteristics and other key points. All changes to the manuscript are shown in red text.

2 Revision has been made according to the suggestions of the reviewer

(1) *This is an interesting case of an entity not described before. The following points are provided for its improvement (2-5).*

(2) *Serum glucagon level should be tested repeatedly and dynamically especially after the biopsy because it was not always 66 pmol/L.*

Response: We agree with this comment, to better illustrate the serum glucagon levels we have added Table 1 to the manuscript showing all readings taken (page 5, page 18).

(3) *The clinical manifestation of the patient could be described in more detail. The only symptom of abdominal pain might be compared in features with other cases and stated about the management in the last decade.*

Response: We agree with these comments. We have added to the case description (page 5).

Indeed the only symptom was non-specific diffuse abdominal pain and it should be noted that the patient denied having any additional symptoms potentially related to a pancreatic tumor when asked. The symptoms of our patient have now been compared with those of other patients (page 8, 19).

(4) *Had the gall stone ever be detected in the past?*

Response: For 8 years our patient experienced non-specific diffuse abdominal pain with no pathology evident. During these 8 years the patient underwent repeated extensive investigations with a complete gastrointestinal diagnostic work up including abdominal ultrasound, CT, MRI, upper GI endoscopy and lower GI endoscopy and standard laboratory analysis. These investigations had the repeated finding that there was no pathology evident. Then in 2009, two

years prior to referral to our centre, gall stones were detected by abdominal ultrasound. We have edited the manuscript to clarify this (page: 5).

(5) *Are there other mutations in the GCGR gene related to this condition? Future study on this entity of disease can be suggested.*

Response: Yes, although they are very rare. The mutations in the GCGR related to this condition are described on page 10 and page 19. We agree that further study of the disease would be of benefit to patients, we have added a sentence to this effect (page 12).

3 Figures 1-3 have been attached as individual ppt. files so that fonts and lines can be edited

We would like to thank the reviewer and editor for their very helpful comments.

Thank you again for considering our manuscript for publication in the *World Journal of Gastrointestinal Surgery*.

Yours Sincerely,

A handwritten signature in blue ink, appearing to read 'A. Frilling', with a small flourish at the end.

Professor Andrea Frilling MD, PhD, FACS, FRCS, FEBS

Professor of Surgery

Chair in Endocrine Surgery

Consultant Surgeon

Department of Surgery and Cancer

Imperial College London

Hammersmith Campus

Du Cane Road

London W12 0HS, UK

Telephone: +44 (0) 20 33133210

Email: a.frilling@imperial.ac.uk

www.imperial.ac.uk