Title: A CASE OF MALIGNANT INSULINOMA RESPONSIVE TO SOMATOSTATIN ANALOGS TREATMENT

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Author’s response to reviews:

REVIEWER 1

We thank the reviewer for the helpful suggestions to improve our manuscript.

Page 3 The sentence about the association between MEN-1 and malignant insulinoma has been deleted. We thank the reviewer for addressing this issue. A modified sentence has been added in the Background.

Page 4, Case Presentation. It has been clarified that 70 mg/dl is not a low glucose level.

Page 4-5 Case Presentation. The short octreotide test has been described, as requested. It has been performed according to reference 10.

Page 5. Case Presentation. It has been clarified that a good control of hypoglycaemia meant normalization of blood glucose levels by glucometer measurement, without hypoglycemic episodes, as well as disappearance of symptoms
The role of 111-In-octreotide scintigraphy has been rephrased. Other imaging techniques, in particular 68Ga-DOTATATE PET/CT and GLP-1 receptor scintigraphy have been discussed and specific references added.

The text has been reviewed by a native speaker (Mrs. Julia, United Kingdom)

REVIEWER 2

We thank the reviewer for the interest in our case report.

Table 1 has been modified, as requested. The headings of the tables have been made more informative. Table 2 has been deleted, according to another reviewer and the results have been moved to the text.

Arrows have been added in the figures, in order to indicate foci of interest

Case reports and literature on insulinomas treated with somatostatin analogs (ref 27-31) have been added in the Discussion.

REVIEWER 3

We thank the reviewer for the helpful and detailed suggestions.

There are similar, yet a few, cases of insulinomas treated with somatostatin analogs in the literature. Case reports and literature on insulinomas treated with somatostatin analogs (ref 27-31) have been added in the Discussion. Admittedly, if we limit the search to malignant insulinomas, the case we described presents a very rare situation. One peculiarity is represented by the choice of using short acting octreotide, in agreement with the surgeon, in order to avoid any possible pharmacological interference caused by long acting formulations at the time of surgery, which was performed shortly after the diagnosis. Honestly, we believe that the case we presented can add some information that may be helpful for clinicians dealing with this rare tumor.

References on the characteristics of malignant insulinomas have been added (ref 4-7)

Only short acting octreotide was used during the short time occurred between diagnosis and surgery.
The reviewer is certainly right about the comment on the use of the word “insulinoma” based on the fasting and glucagone test. Therefore the word insulinoma has been deleted in such a context. (Case Presentation, page 4).

The reference range of the hormonal parameters has been added, as requested (text and tables).

The word “insulinemia” has been changed into “insulin level”

The reference indicating the interpretation of short octreotide test is indicated (ref 10)

A figure showing the pancreatic histological findings has been added (fig. 3)

Table 2 has been deleted, as requested. The results and the interpretation of the glucagone test have been detailed in the text (Case Presentation, pag 4).

The pathological findings in fig 1 and 2 have been indicated with arrows, according to the request of the reviewer.

In table 1 the meaning of h 24 has been clarified.

The sentence regarding the description of CT scan (“..without signs of infiltration”) has been modified.