Author's response to reviews

Title: Hypoglycemia mediated by paraneoplastic production of Insulin like growth factor - 2 by malignant renal solitary fibrous tumor - clinical case and literature review

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Author's response to reviews: see over
Dear Editor,

Thank you for considering our manuscript titled “Hypoglycemia mediated by paraneoplastic production of Insulin like growth factor – 2 from a malignant renal solitary fibrous tumor – clinical case and literature review” for BMC Endocrine Disorder.

The authors would like to thank the reviewers for their careful review and important suggestions that has improved the quality of this manuscript.

Please find below point-by-point response (in blue) to the concerns raised by the reviewers.

Thank you.

Ameer Khowaja MD

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Reviewer: Atsunari Kawashima

Reviewer's report:

(Major Compulsory Revisions)

1. Please show the figures of HE stained sections.

   We have included H&E stained image in the revised manuscript submission.

2. Could you modify your table.1 including post-operative data?

   We appreciate referee’s comment and have included post-operative level of IGF-1 and IGF-2 as a separate table in revised manuscript.

3. You should exclude the probability that big IGF-II induced NICTH if you want to conclude that IGF-II not big IGF-II secreted by tumor induced NICTH. You should contact the authors (Ref 41 or Hizuka et al (Endocr J 45: 61-65. 1998)) to analyze your samples (serum, tissue sample) using western immunoblotting and immunohistochemistry.

   Authors acknowledge the reviewer’s concerns regarding ruling out “big IGF-2”. Likelihood of big IGF-2 increases when there is a high clinical concern for NICTH and normal IGF-2 levels. In our case, patient already had very high IGF-2 level, making likelihood of Big IGF-2 relatively low. Moreover use of IGF-1 to IGF-2 ratio has been suggested in the literature since assay for Big IGF-2 is not available clinically and being used for research purposes only. We have discussed this in our manuscript.
Reviewer: Teresa Mezza

Reviewer's report:

In this manuscript, the authors report a case of NICTH associated with paraneoplastic IGF-2 production in a 60 years old male with imaging showing a large right suprarenal mass. The patient was undergone to right nephrectomy with resection of the mass, malignant solitary fibrous tumor was harvested.

Major points:

As the authors summarized in table 2, several cases of NICTH producing IGF2 has been already reported. However, whether new aspects in the disease pathogenesis and natural history will come up, new cases will be appreciated for reporting. In this report, the authors should emphasize new aspects of the disease to suggest relevance and importance for publication.

We appreciate referee’s comment. IGF-2 induced hypoglycemia remains uncommon. In this manuscript, authors report another case that will contribute to the existing body of literature on current subject along with an extensive literature review. This case report and literature review will help clinicians in recognizing different causes and presentations of this rare cause of hypoglycemia and assist in devising a systematic approach along with considering other differentials, diagnostic modalities and treatment options.

Have the authors performed a simple OGTT to exclude hyperinsulimenia and reactive hypoglycemia? Is the insulin, as well as C-peptide, reported in table 1 in fasting or fed state?

We did not perform OGTT and post prandial insulin level because on the basis of history, a concern for reactive hypoglycemia was very low (due to lack of postprandial symptoms and presence of fasting hypoglycemia). As above, the c-peptide and insulin levels in Table 1 were performed in a fasting state (overnight fast), and Table 1 has been updated to reflect that.

Have the authors confirmed the IGF2 assay? Several issues could affect not-routinely assay like IGF2.

IGF-2 levels were performed by Quest diagnostics, which is a laboratory service provider not affiliated with our institution. Levels were determined using an immunoradiometric assay with an analytic sensitivity of 150 ng/mL.

IGF-1 and insulin are similar in homology to IGF-2, and radiometric assays are subject to interference in the presence of proteins with similar homology, but both IGF-1 and insulin were undetectable, thus allaying any concerns regarding assay reliability and interference. Radiometric assays also are subject to interference from circulating antibodies. However, our patient did not have a history of any autoimmune conditions.