

Dear Editors,

Dear Editors and Reviewers,

We would like to thank the reviewers for their very valuable comments and suggestions. And we have revised our manuscript according to the reviewer comments. We have also revised the manuscript in terms of style of grammar. A point-to-point response to the reviewer comments follows.

Yours sincerely,

Ni Chen

Reviewer #1: **Conclusion:** Minor revision

Major Comments:

Q1. The authors should underline in the discussion with an additional sub-paragraph the fundamental role of diagnostic imaging in such peculiar clinical cases to stage as well as to characterize tumor lesions. In particular, the role of total-body PET/CT with FDG should be underlined in patients with multiple tumor sites as occurred for example in patients described by Klain et al. (Klain M, Maurea S, Gaudieri V, Zampella E, Volpe F, Manganelli M, Piscopo L, De Risi M, Cuocolo A. The diagnostic role of total-body 18F-FDG PET/CT in patients with multiple tumors: a report of the association of thyroid cancer with lung or renal tumors. Quant Imaging Med Surg. 2021 Sep;11(9):4211-4215. doi: 10.21037/qims-21-36. PMID: 34476200; PMCID: PMC8339643).

A1. Thanks for the advice. We have added a paragraph in the discussion the fundamental role of diagnostic imaging in the revised manuscript and cited the article recommended. As the reviewer mentioned, total-body PET/CT with 18F-fluorodeoxyglucose (18FDG) would be very helpful in diagnose of multiple

primary tumors as our case, but regrettably the patient refused to undergo PET/CT and MIBG examinations, although the surgeon recommended these tests. Please check the revision details in the discussion section.

[Revised] in DISCUSSION section

Imaging techniques may be beneficial for initial diagnosis of multiple tumors. Patients with multiple primary tumors should undergo ^{18}F -fluorodeoxyglucose (F-FDG) positron emission tomography (PET)/CT to detect a wide range of unexpected malignant tumors^[26]. Some special imaging techniques are particularly helpful for diagnosing CCRCC and PCC. A recent study showed that MRI is a feasible tool for the diagnosis of CCRCC and may predict the Fuhrman grade of CCRCC^[27]. Radiotracers such as radioiodine labelling metaiodoenzylguanidine (MIBG) or ^{68}Ga labelling somatostatin analogs could help diagnose PCC ^[28-29]. In our study, the patient showed typical imaging features of CCRCC and PCC on an enhanced CT scan, but regrettably she refused to undergo PET/CT and MIBG examinations, although the surgeon recommended these tests. In the present case, although examination of images was very beneficial for diagnosing this condition before surgery, the rare diagnosis of TTM was still based on pathological investigations.

Q2. Furthermore, the innovative role of radiomics to characterize CCRCC should mentioned according to experience by Stanzione et al. (Stanzione A, Ricciardi C, Cuocolo R, Romeo V, Petrone J, Sarnataro M, Mainenti PP, Improta G, De Rosa F, Insabato L, Brunetti A, Maurea S. MRI Radiomics for the Prediction of Fuhrman Grade in Clear Cell Renal Cell Carcinoma: a Machine Learning Exploratory Study. J Digit Imaging. 2020 Aug;33(4):879-887. doi: 10.1007/s10278-020-00336-y. PMID: 32314070; PMCID: PMC7522138).

A2. Thanks for your suggestion. Just as the recommended article describes, MRI is a feasible tool for the diagnosis of CCRCC and may predict the Fuhrman grade of CCRCC. We have cited this viewpoint in our revision. Please check the details in the discussion section.

Q3. Finally, the role of specific radiopharmaceuticals to characterize PCC, such as labeled MIBG and/or somatostatin analogs, should be also discussed, as reported by Lastoria et al. (Lastoria S, Maurea S, Vergara E, Acampa W, Varrella P, Klain M, Muto P, Bernardy JD, Salvatore M. Comparison of labeled MIBG and somatostatin analogs in imaging neuroendocrine tumors. Q J Nucl Med. 1995 Dec;39(4 Suppl 1):145-9. PMID: 9002775) and by Maurea et al. (Maurea S, Caracò C, Klain M, Mainolfi C, Salvatore M. Imaging characterization of non-hypersecreting adrenal masses. Comparison between MR and radionuclide techniques. Q J Nucl Med Mol Imaging. 2004 Sep;48(3):188-97. PMID: 15499292).

A3. Thanks for your suggestion. Radiotracer such as radioiodine labelling metaiodoenzylguanidine (MIBG) or 68Ga labelling somatostatin analogs could help diagnose PCC. We've cited the literature in our revision. Please check the details in the discussion section.

Q4. Minor comments: The abbreviation PCC needs to be initially expanded.

A4. PCC is the abbreviation of pheochromocytoma. We have revised and defined this abbreviation in the revised manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

Q1. Abstract section: Background: Please describe the definition of the abbreviations "RCC" and "PCC", since it is mentioned for the first time in the text.

A1. Thanks for your reminder. RCC is the abbreviation of renal cell carcinoma, and PCC stands for pheochromocytoma. We have revised and defined these abbreviations in the manuscript.

Q2. Case presentation: Please clarify the term "aggravating abdominal pain" and if it is the correct term, specify which stimulus "aggravates" the abdominal pain and the characteristics of abdominal pain. Please specify the type of computed tomography (CT). contrast-enhanced CT scan? adrenal protocol?

A2. Thank you for your question. We revised the ambiguous term "aggravating abdominal pain" as the following: The patient had recurrent chronic dull pain in her left abdomen for six months without showing any obvious causes. She did not receive any treatment until the pain became unexpectedly aggravated in the last one month, with nausea and difficulty in defecating. The detailed description is revised in the history of present illness. The patient received the enhanced computed tomography (CT) of the upper and lower abdomen. The corresponding revision was in the imaging examination section.

Q3. Was the diagnosis of pheochromocytoma made in the postoperative period? Please describe the medication that the patient was receiving before surgery.

A3. Before surgery, elevated serum normetanephrine (NMN), dopamine (DA) and 3-methoxytyramine(3-MT) were detected by the laboratory examination. Clinicians did consider the initial diagnosis of PCC. The patient was administered

phenoxybenzamine hydrochloride tablets at a dose of 10 mg twice daily for seven days before surgery. Please check the details in the treatment section.

Q4. Did the patient receive alpha-blocker therapy prior to surgery to prevent complications associated with pheochromocytoma?

A4. As we answered in Q3, the patient did receive alpha-blocker therapy. She received phenoxybenzamine hydrochloride tablets at a dose of 10 mg twice daily for seven days before surgery.

Q5. I am surprised/concerned that having found a left adrenal incidentaloma, the medical team did not request measurement of plasma/urinary metanephrines prior to surgery.

A5. Thanks for your reminder. As replied in Q3, we revised and clarified details in our manuscript in the section of laboratory examination: Before surgery, laboratory tests showed that dopamine (DA) level was increased to 6.26 nmol/L, which was much higher than the standard value of 0.31 nmol/L. Normetanephrine (NMN) level was 0.84 nmol/L, much higher than the standard value of 0.71 nmol/L. The 3-methoxytyramine(3-MT) level was increased to 239.82 pg/ml, exceeding the 18.4 pg/ml standard value. The patient's serum potassium was 3.86 mmol/L, which was within the standard range.

Q6. Discussion: Very succinct. It seems only like an article review and does not discuss the clinical case presented.

A6. Thanks for the suggestion. We've revised the discussion and added some discussion of imaging and clinical case presented. Please check the details in discussion section.

science editor:

Q1. A case showing CCRCC metastasis to PCC in forming of tumor-to-tumor metastasis. But the definition of the abbreviations "CCRCC" and "PCC" were not mentioned in the text.

Language Quality: Grade C (A great deal of language polishing)

Scientific Quality: Grade C (Good)

A1. We have revised and defined the abbreviations in the revised manuscript. PCC is the abbreviation of pheochromocytoma, and CCRCC represents the acronyms of clear cell renal cell carcinoma.

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted.

I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents.

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A: We sincerely appreciate your time and efforts in our manuscript. We have checked and confirmed the figures presented in the manuscript. All the figures were arranged in the PowerPoint document attached. You may check the files we re-upload.