Author’s response to reviews

Title: Metatarsal metastasis from clear cell renal cell carcinoma: a case report and literature review.

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Author’s response to reviews:

Dear editor

Thank you very much for your email dated November 2, 2019, and the referees’ reports. Based on your comments and requests, we have made some modification on the original manuscript. Here, we attached the revised manuscript in which all changes made to the text were in red so that they may be easily identified. We hope that the revised manuscript is acceptable for publication.

Thank you.

With best wishes,

Yours sincerely,

Helin Feng

Replies to # Technical Comments

1. Review by a native English speaker will be needed.

Response: Thanks for your positive suggestions, we have thoroughly reviewed and revised the manuscript again and it seems that there is no problem.
2. Abstract: In the "Case presentation" section of the abstract, first sentence, it would be helpful to specify that this patient presented with “isolated” metastasis to his right metatarsal bone from clear cell renal cell carcinoma.” It would also be helpful if the abstract mentioned the time from nephrectomy to detection of metastasis.

Response: Thanks for your positive suggestions, we have re-written the case presentation of the abstract according to the Editor’s suggestion. We adjusted the text in the manuscript.

The first sentence of "Case presentation" section in abstract now is:

We report a 68-year-old man with solitary metatarsal metastasis after 26 months of diagnosis of renal clear cell carcinoma.

3. Along the lines of reviewer #1’s original comments, I still feel the wording of the abstract conclusion can be improved. I would recommend that focus should of the abstract conclusion should be that clinicians should be aware of history of renal cell carcinoma and that a high index of suspicion is important in these patients when they have unresolving bony pain or swelling. To add, I think the message can be generalized beyond the foot since RCC can metastasize virtually anywhere. Also, I would suggest removing "male" from the abstract conclusion. Although male sex is a risk factor for RCC, clinicians should be equally careful in both males and females presenting with symptoms compatible with metastatic RCC.

Response: Thanks for your positive suggestions, we have re-written the conclusion of the abstract according to the Editor’s suggestion. We adjusted the text in the manuscript.

The "Conclusion " section abstract now is:

Clinicians should be aware of history of renal cell carcinoma. When receiving patients with clear cell renal cell carcinoma who have unresolving bony pain or swelling, the clinicians should always keep in mind the possibility of bone metastasis of renal cell carcinoma.

4. In the second paragraph of the case presentation, it is stated that "After thorough examination and evaluation, no other distant metastatic lesion was found in the patient." I would request the authors are more specific as to the re-staging investigations performed. At minimum cross-sectional imaging of the chest, abdomen and pelvis are required.

Response: In the initial diagnosis of renal cell carcinoma, cross-sectional imaging of the chest, abdomen and pelvis was carried out without abnormality.

5. In the discussion section, it is stated that the "best treatment for a single metastasis is always surgical excision..." This is a controversial statement. If there is a prolonged time from nephrectomy to detection of metastasis, then metastasectomy is likely appropriate, as in this case. However, if the time from nephrectomy to development of
metastasis is short, this may suggest a poor prognosis and many clinicians would proceed with systemic therapy rather than surgery because further metastases are so likely to show up elsewhere. I would suggest revising this statement.

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

The second paragraph of the discussion and conclusion now is:

As no therapeutic standard or guideline currently exists for RCC with bone metastasis. The median survival time of RCC with bone metastasis was usually below 24 months [16]. Acrometastases are often associated with extensive metastasis in other sites, so the prognosis is poor. The treatment is usually palliative and needs to be adapted to each patient’s individual condition. Relief of pain is often the therapeutic goal. Palliative treatment of bone metastases has always been conservative: using adiotherapy, chemotherapy, immunotherapy, targeted therapy, bisphosphonates and analgesics [17]. More recently, minimally-invasive techniques, including ethanol, laser, microwave, cryo-ablation and radiofrequency ablation, have been used for painful bone lesions [18-22]. Surgical resection of bone metastasis from RCC has been reported to improve the prognosis of patients and even better for solitary metastasis if feasible [23]. These are all met in our case. We believe that the best treatment for a single metastasis is always surgical excision, if there is a long time from nephrectomy to the detection of isolated metastasis.

Replies to Reviewers

We appreciate the reviewers’ comments which have helped us significantly improve the scientific quality of this manuscript. Here are the point-to-point responses to reviewers’ comments below.

Reviewer #1:

I continue to suggest review of the manuscript by a native English speaker, as there are multiple instances of minor grammatical errors with improper use of plurals, articles and prepositions.

Response: Thanks for your positive suggestions, we have thoroughly reviewed and revised the manuscript again and it seems that there is no problem.

Special thanks to you for your good comments.

Reviewer #2:
1. Minor: I would suggest introducing the RCC acronym in the main body of the text (Background) and use it consistently throughout the paper.

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

2. There are several remaining grammatical errors that should be fixed before publication (see suggestions below).

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

3. There are several remaining grammatical errors that should be fixed before publication (see suggestions below).

Abstract:

Consider the following grammatical changes:

We report a case of a 68-year-old man with metastasis to a metatarsal bone…

After reviewing the medical records, we found that this patient had a history of…

These findings confirmed the patient had a metatarsal metastasis from…

Clinicians should fully understand the patient's past medical history, especially in the case of foot swelling and pain in male patients with a history of clear cell renal cell carcinoma. The possibility of a foot bone metastasis should always be considered.

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

Keywords: foot bone

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

Background:

Consider the following grammatical changes:

Line 36/37: …such as the spine and pelvis.

Line 38/39: Bone metastasis of the foot…

Line 43/44: …and review the related literature.
Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

Case Presentation:

Consider the following grammatical changes:

Line 55-59: The patient had a history of a mild right foot sprain that caused pain a year ago. Initially, the pain was relieved after rest, but progressed with worsening pain and swelling after daily activities.

Line 2-3: …the patient's right foot was continuously swollen with worsening, severe pain that limited ambulation.

Line 15: …suspicious for underlying malignancy.

Line 20: After reviewing the medical history, we discovered that the patient had a history of a large left renal mass, discovered in April of 2017.

Line 29: Subsequently, work-up was negative for metastatic disease and a radical nephrectomy was performed.

Line 39: Therefore, in the context of a known primary renal cell carcinoma, a metatarsal metastasis was suspected.

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.

Discussion and Conclusion:

Consider the following grammatical changes:

Line 47: During the 1-year period, the patient developed intermittent swelling…

Line 51: Diagnostic delay may lead to pathological fractures; therefore, metastatic bone disease of the foot…

Line 28: …using radiotherapy…

Line 59: Even though acrometastasis is rare, this diagnosis should be considered in any patient with a history of RCC, particularly male patients, with local pain and swelling. Appropriate clinical and radiographic evaluation of these patients is essential in order to offer timely local therapy that may improve prognosis and enhance patient quality of life.

Response: Thanks for your positive suggestions, we adjusted the text in the manuscript.