

Peer Review File

Article information: <https://dx.doi.org/10.21037/jgo-23-336>

Reviewer A

The authors describe a very interesting case of advanced hepatocellular carcinoma with skin metastases treated with camrelizumab. There is no precedent like this case, and this case report is worthy of publication. However, there are a few things that need to be corrected to improve this paper.

#1. In line 70-71, what does "markings" mean? Distant metastasis in lung or not? If so, the authors described "The patient was diagnosed with primary hepatocellular carcinoma with lung metastasis and chronic viral hepatitis B infection." It would be easier for the reader to understand if you could add images of the patient before TACE treatment at the time of initial diagnosis, if available.

Response: Thanks for the reviewer's suggestion. We will modify "Chest CT showed increased lung texture in both lungs"

#2. I think Figure would be more understandable to the reader if the image were enlarged a little more, and if arrows were placed at the location of the tumor, etc.

Response: We have modified it in accordance with it

Reviewer B

1) First, the abstract needs some revisions. In the background, the authors need to describe the potential clinical contribution of this case report and explain why the current case deserved to be reported. In the case presentation, the authors need to briefly describe the disease history, treatment process, the clinical presentations and progression and characteristics of nasal alar metastasis and RCCEP, and treatment and prognosis of the nasal alar metastasis. The conclusion needs more detailed comments for the clinical implications of the findings from this case such as how to achieve early diagnosis and early treatment.

Response: Thanks for the reviewer's suggestion. We will add "Facial skin metastasis is an exceptionally uncommon occurrence in hepatocellular carcinoma (HCC). It can be easily mistaken for a prevalent complication known as RCCEP, particularly when it manifests as a persistently enlarging tumor-like mass. This case report highlights a prototypical instance where a metastasis in the nasal alar region of HCC was mistakenly diagnosed as RCCEP during immunotherapy. The findings of this report hold significant clinical value in guiding the management of larger RCCEP lesions encountered during immunotherapy." in the background.

In the case presentation, we added the disease history, treatment process, the clinical presentations and progression and characteristics of nasal alar metastasis and RCCEP, and treatment and prognosis of the nasal alar metastasis as follows:

In the The patient is a male with a history of hepatitis B. In October 2015, he was diagnosed with hepatocellular carcinoma (HCC). Over the course of his treatment, he underwent a series of interventions including 9 transarterial chemoembolization (TACE) procedures and 1 microwave ablation treatment between October 2015 and April 2020. In April 2020, he commenced treatment with ramucirumab (200mg every 3 weeks). However, during the third treatment cycle, the patient experienced RCCEP, predominantly affecting the head, neck, trunk, and limbs. To address this, sequential administration of apatinib was initiated, resulting in the gradual regression of RCCEP in these areas. Unfortunately, the metastatic lesion in the nasal alar region continued to grow, exhibiting a tumor-like appearance. On January 25, 2021, surgical resection was performed to remove the nasal alar lesion, and subsequent pathological examination confirmed it as a liver metastasis. Post-surgery, radiation therapy was administered to effectively manage the remaining lesion in the nasal alar region. Importantly, the treatment of the nasal alar metastasis did not hinder the comprehensive management of HCC.

We have added detailed for the clinical implications of the findings as follows: During the course of immunotherapy for HCC, the emergence of a larger RCCEP lesion that does not show signs of regression even with vigorous treatment raises the suspicion of skin metastasis. To obtain a definitive diagnosis, an early pathological biopsy is crucial. If confirmed as a metastatic tumor, prompt consideration should be given to implementing curative surgical resection.

The findings from this case have important clinical implications, particularly regarding the early diagnosis and treatment of skin metastasis during HCC immunotherapy. It is crucial to closely monitor patients undergoing immunotherapy for the emergence of larger RCCEP lesions that do not show regression with standard treatment. In such cases, a high index of suspicion for skin metastasis should be maintained, and an early pathological biopsy should be performed to confirm the diagnosis.

To achieve early diagnosis, regular imaging surveillance should be conducted, and any suspicious skin lesions should be promptly evaluated. Dermatological examinations can aid in detecting early signs of skin metastasis. Additionally, educating both healthcare providers and patients about the possibility of skin metastasis during HCC immunotherapy can help raise awareness and facilitate early detection.

Regarding early treatment, if skin metastasis is confirmed, immediate intervention is essential. Early initiation of curative surgical resection can improve patient outcomes by removing the metastatic lesion and potentially preventing further spread. Multidisciplinary collaboration among oncologists, dermatologists, and surgeons is crucial to develop individualized treatment plans and ensure timely intervention.

- 2) Second, in the introduction of the main text, please have a brief review on the incidence rate, site, clinical presentation of nasal alar metastasis and RCCEP and have comments on the harmful consequences of misdiagnosis and mistreatment of nasal alar metastasis. The authors need to have comments on the rarity and unique clinical contribution of this case.

Respond: Thanks for the reviewer's suggestion. We accept your suggestions with all sincerity.

We have added: "The occurrence of nasal alar metastasis in HCC is an extremely rare phenomenon, and there is currently a lack of relevant literature documenting such cases. On the other hand, RCCEP has been identified as the most frequent adverse reaction associated with monotherapy using ramucirumab, accounting for approximately 77% of cases. The commonly affected areas include the head, neck, trunk, and limbs, and RCCEP is typically classified into five distinct types: erythematous, pearly, mulberry-like, patchy, and tumor-like (as discussed in the relevant section). Misdiagnosing nasal alar metastasis as RCCEP can potentially lead to continuous tumor progression, significantly impacting the patient's long-term prognosis. Despite an extensive review of the literature, no previous reports have been found documenting the misdiagnosis of nasal alar metastasis as RCCEP. Hence, this case report holds exceptional value due to its rarity and unique findings."

- 3) Third, in the case presentation of the main text, please use a timeline figure to briefly describe the history, treatment, presentation and changing patterns of nasal alar metastasis and RCCEP, pathological findings, treatment for nasal alar metastasis and response, and long-term prognosis of this case.

