

## Peer Review File

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### Reviewer A

**Comment 1:** Since RCCEP with camrelizumab is common, it is better to add in the title “improved by anlotinib” ,which is the point of this case.

**Reply 1:** Considering the Reviewer’s suggestion, we have modified the title of the paper which is marked in red (see Page 1, line1).

The modified title of the paper is as follows: Anlotinib Improved the Reactive Cutaneous Capillary Endothelial Proliferation Induced by Camrelizumab: A Case Report

**Comment 2:** How do you plan for the future, should anlotinib be continued after RCCEP improves, can it be discontinued, or will it get worse if stopped?

**Reply 2:** As described in Page 2, line23-25. The patient was treated with oral anlotinib (8mg, once a day). After 5 days of treatment, the symptoms of RCCEP gradually eased, and the patient was discharged. And in Page 5, line94-97. The patient was treated with oral anlotinib hydrochloride capsule 8mg once a day. The patient’s rash improved significantly, the papule became lighter and the size atrophied, and no new RCCEP was found on other parts of the body.

With the treatment of anlotinib, the symptoms of RCCEP eased on 12 September 2021. And after another 2 days treatment then anlotinib was discontinued. On 14 September 2021, the patient was discharged, no RCCEP occurred during the later

re-hospitalization for treatment.

And we added the content when the symptoms of RCCEP relieved and how long did we administer anlotinib in the paper which is marked in red (see Page 5, line95, 97).

The added contents are as follows:

On 12 September 2021, the patient's rash improved significantly, the papule became lighter and the size atrophied, and no new RCCEP was found on other parts of the body. And after another 2 days treatment then anlotinib was discontinued.

**Comment 3:** Please check the following terms: Page 3, 64-66

Metastasis to multiple lymphocytes, T1N4, tumor.

**Reply 3:** We are very sorry for our mistake, that the correct tumor stage of the patient was T4N1. And we have revised the error content which is marked in red (see Page 4, line71).

**Comment 4:** Check the dosage units of Paclitaxel albumin bound.

**Reply 4:** We are sorry to make a mistake when inputting the dosage units of Paclitaxel albumin bound, that the correct unit was milligram (mg). We have corrected it and marked in red (see Page 4, line73, 75 and 85).

**Comment 5:** Figure 2(B) says "He had a rash under his right eye", but in the photo it appears to be on the left eye. Please confirm whether this is an error or the image is inverted.

**Reply 5:** We are sorry for the mistake. We reviewed the patient's cases and consulted the doctor; the rash was under the patient's left eye. We have corrected it and marked

in red (see Page 5 line90, Page 13, line281).

**Comment 6:** If you have images, you should include any images that RCCEP has improved.

**Reply 6:** The comment is very helpful for our study, however we did not get the images that RCCEP has improved, and the patient had discharged.

**Comment 7:** Other reports of treatment showing efficacy against RCCEP should be included in the DISCUSSION. If anlotinib is easier to use in practice than other reports, this report will be more important.

**Reply 7:** The management of RCCEP caused by camrelizumab is based on Guidelines for the clinical application of new anti-tumor drugs, 2019 drawn up by National Health Commission of People's Republic of China and Consensus on the clinical diagnosis and treatment of reactive skin capillary hyperplasia caused by carrelizumab published by Chinese scholars (see reference 14, 15).

Many effective methods of treatment RCCEP could be found in other reports, so that we did not show in our paper. Referring to the relevant literature and the possible mechanism of RCCEP, combined with the actual situation of patients, we chose anlotinib to deal with the RCCEP induced by camrelizumab. We report a case that anlotinib improved RCCEP induced by anti-PD-1 blockade camrelizumab which may provide a potential management to reduce the adverse reactions who are treated with camrelizumab. If anlotinib is easier to use in practice than other reports need more validation.

14. Consensus on the clinical diagnosis and treatment of reactive skin capillary

hyperplasia caused by carrelizumab. Chinese Clinical Oncology 2020;25:840-8.

15. Guidelines for the clinical application of new anti-tumor drugs, 2019. Journal of Multidisciplinary Cancer Management (Electronic Version) 2020;6:16-47.

**Comment 8:** Is the combination of camrelizumab and anlotinib a common practice in your country?

**Reply 8:** The combination of camrelizumab and anlotinib is a common practice. Anlotinib combined with Anti-PD-1 antibodies usually used to therapy in patients with advanced solid tumors (1, 2, 3, 4). The combination of anlotinib and anti-PD-1 antibodies demonstrated promising durable antitumor efficacy with acceptable toxicity in patients with various advance tumors. And in our hospital, several patients received this treatment.

1. Zhou N, Jiang M, Li T, et al. Anlotinib combined with anti-PD-1 antibody, camrelizumab for advanced NSCLCs after multiple lines treatment: An open-label, dose escalation and expansion study. Lung Cancer 2021;160:111-7.

2. Wang Y, Shi X, Qi Q, et al. Safety of Anlotinib Capsules Combined with PD-1 Inhibitor Camrelizumab in the Third-Line Treatment of Advanced Non-Small-Cell Lung Cancer and Their Effect on Serum Tumor Markers. 2021;2021:2338800.

3. Yuan M, Zhu Z, Mao W, et al. Anlotinib Combined With Anti-PD-1 Antibodies Therapy in Patients With Advanced Refractory Solid Tumors: A Single-Center, Observational, Prospective Study. Front Oncol 2021;11:683502.

4. Wang P, Fang X, Yin T, et al. Efficacy and Safety of Anti-PD-1 Plus Anlotinib in Patients With Advanced Non-Small-Cell Lung Cancer After Previous Systemic

Treatment Failure-A Retrospective Study. Front Oncol 2021;11:628124.

### **Reviewer B**

**Comment 1:** What is the most crucial point the authors want to appeal to in this case report? Is that regarding successful treatment with anlotinib for RCCEP? As the authors state in the text that RCCEP is a common adverse reaction of camrelizumab, and does not seem novelty for case reports. Please revise your abstract's conclusion and introduction to explain what you are trying to appeal to clearly.

**Reply 1:** The comment is very helpful for our study, as Reviewer suggested that we have revised our paper to explain successful treatment with anlotinib for RCCEP was the crucial point of our case.

The revised contents are as follows:

#### Abstract

Here we describe a case that anlotinib improved RCCEP induced by anti-PD-1 blockade camrelizumab with some focus on further management of this symptoms.

(see Page1 line16-18)

#### Abstract's conclusion

In conclusion, we have reported a case of RCCEP induced by anti-PD-1 blockade camrelizumab. The patient was given oral anlotinib to relieve the symptoms of RCCEP. Suggesting that anlotinib could be a potential management to reduce the adverse reactions who are treated with camrelizumab. (see Page2 line25-29)

#### Introduction

Anlotinib is a small molecule inhibitor of multiple receptor tyrosine kinases; it has broad-spectrum inhibitory effects on angiogenesis and tumour growth through inhibition of vascular endothelial growth factor receptor (VEGFR) 2 and 3(6). Some reports indicate that combination of anlotinib and anti-PD-1 antibodies demonstrated promising durable antitumor efficacy with hypotoxic in patients with various advance tumors(7). Anlotinib could be a potential management to reduce the adverse reactions that are treated with camrelizumab. (see Page3 line52-59)

6. Gao Y, Liu P, Shi R. Anlotinib as a molecular targeted therapy for tumors. *Oncol Lett* 2020;20:1001-14.

7. Yuan M, Zhu Z, Mao W, et al. Anlotinib Combined With Anti-PD-1 Antibodies Therapy in Patients With Advanced Refractory Solid Tumors: A Single-Center, Observational, Prospective Study. *Front Oncol* 2021;11:683502.

**Comment 2:** Did the authors discontinue the administration of camrelizumab after being diagnosed with RCCEP? And, how long did the authors administer anlotinib?

**Reply 2:** The patient received the immunotherapy with camrelizumab (200mg, every 3 weeks). However, on the fifth cycle of treatment, he happened the RCCEP. With the 5 days treatment of anlotinib, the symptoms of RCCEP eased. And after another 2 days treatment then anlotinib was discontinued.

Refer to Guidelines for the clinical application of new anti-tumor drugs, 2019 drawn up by National Health Commission of People's Republic of China and Consensus on the clinical diagnosis and treatment of reactive skin capillary hyperplasia caused by carrelizumab published by Chinese scholars (see reference 14,

15). Camrelizumab therapy can be continued while the symptoms of RCCEP were less severe. And in this case, the symptoms of RCCEP were less severe and relieved by anlotinib. And the patient received the sixth and seventh cycle immunotherapy with camrelizumab 200mg on 3 October 2021 and 6 November 2021.

14. Consensus on the clinical diagnosis and treatment of reactive skin capillary hyperplasia caused by carrelizumab. Chinese Clinical Oncology 2020;25:840-8.

15. Guidelines for the clinical application of new anti-tumor drugs, 2019. Journal of Multidisciplinary Cancer Management (Electronic Version) 2020;6:16-47.

And we added the content when the symptoms of RCCEP relieved and how long did we administer anlotinib in the paper which is marked in red (see Page5, line95, 97).

The added contents are as follows:

On 12 September 2021, the patient's rash improved significantly, the papule became lighter and the size atrophied, and no new RCCEP was found on other parts of the body. And after another 2 days treatment then anlotinib was discontinued.

**Comment 3:** Did the authors conduct the biopsy for RCCEP?

**Reply 3:** We are very sorry for our negligence, that we did not conduct the biopsy for RCCEP.

**Comment 4:** In lines 132-134, are there any references that support your speculation for the possible mechanism of RCCEP induced by a PD-1 inhibitor?

**Reply 4:** We are sorry for our unclear expression of that part, the possible mechanism

of RCCEP induced by a PD-1 inhibitor from reference 19.

19. Wang F, Qin S, Sun X, et al. Reactive cutaneous capillary endothelial proliferation in advanced hepatocellular carcinoma patients treated with camrelizumab: data derived from a multicenter phase 2 trial. *J Hematol Oncol* 2020;13:47.

**Comment 5:** Is the dose of paclitaxel correct?

**Reply 5:** We are sorry to make a mistake when inputting the dosage units of Paclitaxel albumin bound, that the correct unit was milligram (mg). We have corrected it and marked in red (see Page 4, line73, 75 and 85).