Complete remission of reactive cutaneous capillary endothelial proliferation caused by the programmed cell death-1 inhibitor camrelizumab achieved through thalidomide monotherapy: A case report

CHUNXIU WANG[1], KAIJIAN LEI[1], YUMING JIA[1], ZUXIN JIANG[2] and SHANBING WANG[1]

Departments of [1]Oncology and [2]Orthopedics, The Second People's Hospital of Yibin, Yibin, Sichuan 644000, P.R. China

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Abstract. Reactive cutaneous capillary endothelial proliferation (RCCEP) is a common adverse effect of the anti-programmed cell death-1 (PD-1) monoclonal antibody camrelizumab and usually occurs on the skin. This condition causes bleeding nodules of varying severity depending on disease grade; these affect a person's appearance and quality of life. The exact mechanism remains elusive and its occurrence in visceral organs has not been previously reported, to the best of our knowledge. Furthermore, there is currently a lack of standard, uniform treatments. The present study reported on a patient who experienced RCCEP during treatment with camrelizumab and benefited greatly from thalidomide, which caused no serious adverse events. An elderly Chinese female initially diagnosed with stage II endometrial cancer had previously undergone surgery, radiotherapy and intravenous chemotherapy but developed multiple metastases in the peritoneum and vaginal remnant. The patient was subsequently prescribed camrelizumab after systemic treatment failed. Soon after commencing treatment with this PD-1 inhibitor, the patient developed RCCEP, whereupon oral low-dose thalidomide monotherapy (100 mg nightly) was prescribed. At two weeks after commencing thalidomide, the RCCEP symptoms were alleviated. Based on this patient's successful treatment, it is suggested that low-dose thalidomide may be an alternative intervention for patients with camrelizumab-induced RCCEP.

Introduction

Camrelizumab is an anti-programmed cell death-1 (PD-1) antibody that is uniquely associated with the treatment-related adverse event of reactive cutaneous capillary endothelial proliferation (RCCEP) (1-3). Most RCCEPs occur in the skin (2), where the incidence rate may be as high as 85.7%, as found in one study on patients treated with camrelizumab (4). Although RCCEP is self-limited, it may persist in certain patients with continuous drug use, and only after drug withdrawal, spontaneous atrophy or necrosis may occur and the lesions fall off. RCCEP is classified into five levels by the Chinese National Medical Products Administration (5), namely 'red-nevus-like', 'pearl-like', 'mulberry-like', 'patch-like' and 'tumor-like'. This condition manifests as bleeding nodules and may seriously affect a person's self-image and quality of life. Although there have been numerous studies on the treatment of RCCEP using methods such as laser or surgical resection (5), the lesions may be scattered and numerous, rendering local treatment insufficient. It was previously reported that the incidence of RCCEP is lower in patients receiving anti-angiogenic drugs; however, this notion remains controversial (6). As such, the development of effective treatment regimens for patients with RCCEP is an urgent unmet medical need in the era of immunotherapy.

Thalidomide is a synthetic glutamate derivative that has potential anti-angiogenic and anti-neoplastic effects, although its mechanisms of action in this regard have remained elusive. It may reduce the expression of interleukin (IL)-6, IL-1β, tumor necrosis factor-α (TNF-α), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) or cell surface adhesion molecules in stromal cells (7). Furthermore, thalidomide is able to immunomodulate T cells, enhance anti-plasma cell cytotoxicity of natural killer cells, inhibit cyclooxygenase-2 and induce an anti-angiogenic effect that may potentially lead to appreciable anti-tumor activity (8). A series of studies have indicated that thalidomide has encouraging anti-angiogenic activities in several types of cancer, including prostate cancer and multiple myeloma (9-11). Recently, Song *et al* (12) reported that thalidomide prevents camrelizumab-induced RCCEP. Providing further evidence in support of these findings, the present study reported on a patient with RCCEP who successfully responded to low-dose oral thalidomide (100 mg administered every night).

Correspondence to: Professor Shanbing Wang, Department of Oncology, The Second People's Hospital of Yibin, 268 Nanguang Road, Yibin, Sichuan 644000, P.R. China
E-mail: wangshanbing1984@163.com

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Case report

In September 2018, a 65-year-old Chinese female underwent radical resection of endometrial carcinoma at the First People's Hospital of Yibin (Yibin, China). The pathological diagnosis was International Federation of Gynecology and Obstetrics stage II endometrial serous adenocarcinoma. At two weeks after the surgery, the patient received chemotherapy comprising paclitaxel combined with cisplatin (three cycles) as adjuvant therapy. In July 2020, multiple metastases in the peritoneum and post-surgical remnant of the vagina were detected by magnetic resonance imaging and computed tomography (CT). The patient then received six cycles of albumin paclitaxel and carboplatin chemotherapy. The patient also underwent radiotherapy (volumetric modulated arc therapy; 60 Gy via 25 fractions of 2.4 Gy each), including vaginal brachytherapy (30 Gy via 5 fractions of 6 Gy each). In April 2021, the patient complained of excessive flatulence and loss of appetite; upon examination, adenocarcinoma cells were found in the seroperitoneum. Given this recurrence, the patient underwent intraperitoneal chemoperfusion with carboplatin after having refused intravenous chemotherapy for systemic treatment. At the same time, the patient was prescribed camrelizumab after it was discovered that the tumor was positive for PD-1. After one month, the flatulence and loss of appetite subsided; however, the patient complained that the skin of her face and torso was scattered with several punctured vascular nodules ~1-2 mm in size. The patient's medical timeline is presented in Fig. 1. The CT images prior to and after the treatment for the recurrence are presented in Fig. 2A and B, respectively.

The size and number of angio-proliferations increased during subsequent treatment, with certain nodules erupting when touched (Fig. 3A). Nodules ranged from 1-2 mm in size. Multiple nodules were fused into a pearl of ~3x5 mm and were bright red, soft and hemorrhaging. The patient was therefore diagnosed with RCCEP. There was no obvious improvement despite the patient avoiding scratching or rubbing the nodules and protecting them from any contact. It was decided to prescribe oral thalidomide (100 mg every night). After one month, the RCCEP disappeared (Fig. 3B). Therefore, no discontinuation or dose reduction of camrelizumab was necessary. In May 2021, 1 month after treatment for a second recurrence, the patient's performance status had also improved under a combination of camrelizumab and thalidomide. In April 2022, The patient achieved a complete tumor response and the RCCEP nodules disappeared.

Discussion

Immune checkpoint inhibitors (ICIs), particularly monoclonal antibodies targeting PD-1 or its ligand PD-L1, have produced marked anti-tumor results when used to treat a variety of malignancies (13-16). Despite their effectiveness, however, ICIs are also associated with adverse events. RCCEP is a common side effect of camrelizumab (17-19) that usually occurs on the skin; even low-grade conditions may easily cause bleeding, affecting the patients' appearance and quality of life. Reactive capillary endothelial proliferation has been reported to occur in the oral mucosa (20,21), but there has been no evidence of its occurrence in visceral organs. At present, there are global standards for the classification of adverse reactions of the skin, such as National Comprehensive Cancer Network and European Society for Medical Oncology, but RCCEP is the most common side effect of camrelizumab, which was independently developed in China. Certain other mAb, such as ramucirumab, Tanibirumab, Nivolumab and Pembrolizumab, have also been reported to be associated with cutaneous capillary endothelial proliferation, which is not unique to Cam but varies in terms of the presentation and incidence of RCCEP (22). Therefore, there is only a Chinese standard for the classification of RCCEP. The relationship between immune-related adverse events (irAEs) to immunotherapy and ICI effectiveness is gradually becoming clearer after certain clinical trials found that immunotherapy is more effective in patients who experience such reactions. However, the relationship between cutaneous irAEs and efficacy is elusive or controversial. For instance, Huang *et al* (23) found that, among 228 patients with advanced and metastatic esophageal squamous cell carcinoma treated with camrelizumab, the median survival time of those with RCCEP (n=182) was 10.1 months, while that of patients without RCCEP (n=46) was only 2.5 months. Aso *et al* (24) analyzed the clinical data of 155 patients with advanced non-small-cell lung cancer who were treated with nivolumab or pembrolizumab monotherapy and found that those with adverse skin reactions (n=51) had a higher objective tumor response rate (57 vs. 19%, $P<0.01$) and longer progression-free survival (12.9 vs. 3.5 months, $P<0.01$) than those with no such reactions. The patient with RCCEP described in the present study is still alive and in complete clinical remission. For this reason, it may be hypothesized that patients with RCCEP caused by immunotherapy may be expected to have a better outcome, which aligns with the findings of these other studies. RCCEP may be related to immunotherapeutic efficacy, and even if it occurs in patients who are benefitting from treatment, it is not recommended that immunotherapy is discontinued unless the lesions bleed profusely and affect a person's appearance, as such occurrences may seriously affect a patient's quality of life. It is necessary to increase the immunotherapy compliance rate and avoid interruptions to gain the maximum benefit; as such, the development of effective treatments for RCCEP in the era of immunotherapy is an urgent unmet medical need.

The mechanism of RCCEP remains elusive. It may be caused by over-activation of immune function due to therapy, which interferes with the balance between pro- and anti-angiogenic factors in the skin. $CD4^+$ T-cell activation may be another mechanism; such activation increases Th2 cytokine IL-4 levels, which in turn stimulates the differentiation of $CD163^+$ M2 macrophages and promotes vascular proliferation by releasing VEGF-A (25-27). It has been hypothesized that the inhibition of angiogenic factors is able to reduce the occurrence of RCCEP. Combining ICIs with molecularly targeted drugs such as bevacizumab and apatinib has also been reported to reduce the incidence of RCCEP, indicating that blocking the VEGF ligand-receptor signaling pathway and inhibiting endothelial cell proliferation sufficiently decreases capillary density to prevent the adverse event (28). However, it remains elusive whether anti-angiogenic drugs are able to reverse RCCEP that has already manifested. Furthermore, ICI monotherapy and immunochemotherapy are currently

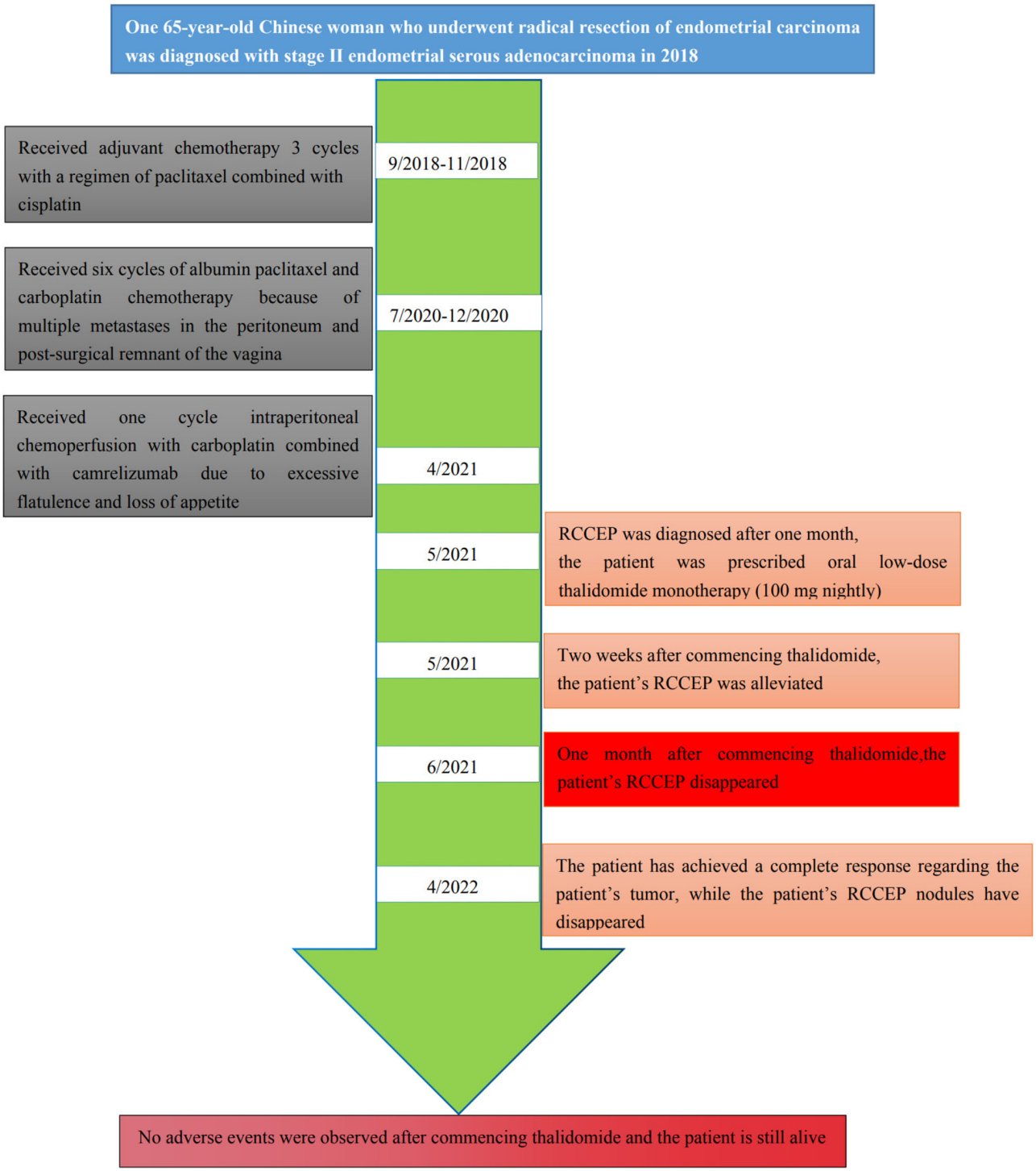

Figure 1. Timeline of interventions and outcomes.

the most widely used regimens (13-16), whereas combining anti-angiogenic agents with ICIs is not yet mainstream and the use of anti-angiogenic drugs to prevent RCCEP remains controversial. At the same time, anti-angiogenic agents should not be routinely used to prevent RCCEP, as this may increase the patient's burden and side effects. Therefore, it may not be reasonable to prescribe expensive anti-angiogenic drugs to treat RCCEP and there is an urgent need for non-invasive and inexpensive drug therapies that may effectively treat RCCEP. To that end, the patient of the present study demonstrated that low-dose thalidomide appears to have a curative effect on RCCEP.

Thalidomide is a synthetic glutamate derivative with two optical isomers, R (dextral) and S (left-handed), at physiological pH, which inhibit VEGF, bFGF and capillary formation in a dose-dependent manner; as such, it exerts an anti-angiogenic effect without changing VEGF-A levels or disturbing the microvessel density in the dermis (29). Thalidomide is able to regulate the secretion of other cytokines induced by TNF-α, thus regulating the immune status of the body (30).

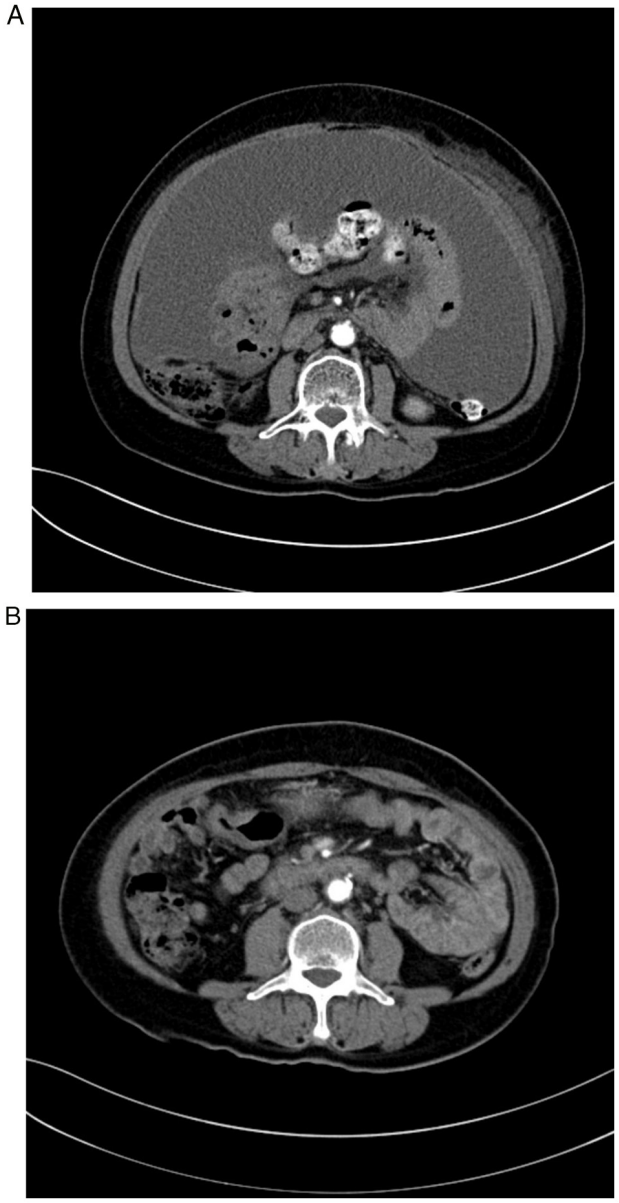

Figure 2. CT of response to combination therapy. (A) Prior to treatment, multiple metastases occurred in the peritoneum and seroperitoneum. (B) After the treatment, peritoneal metastasis and seroperitoneum had disappeared.

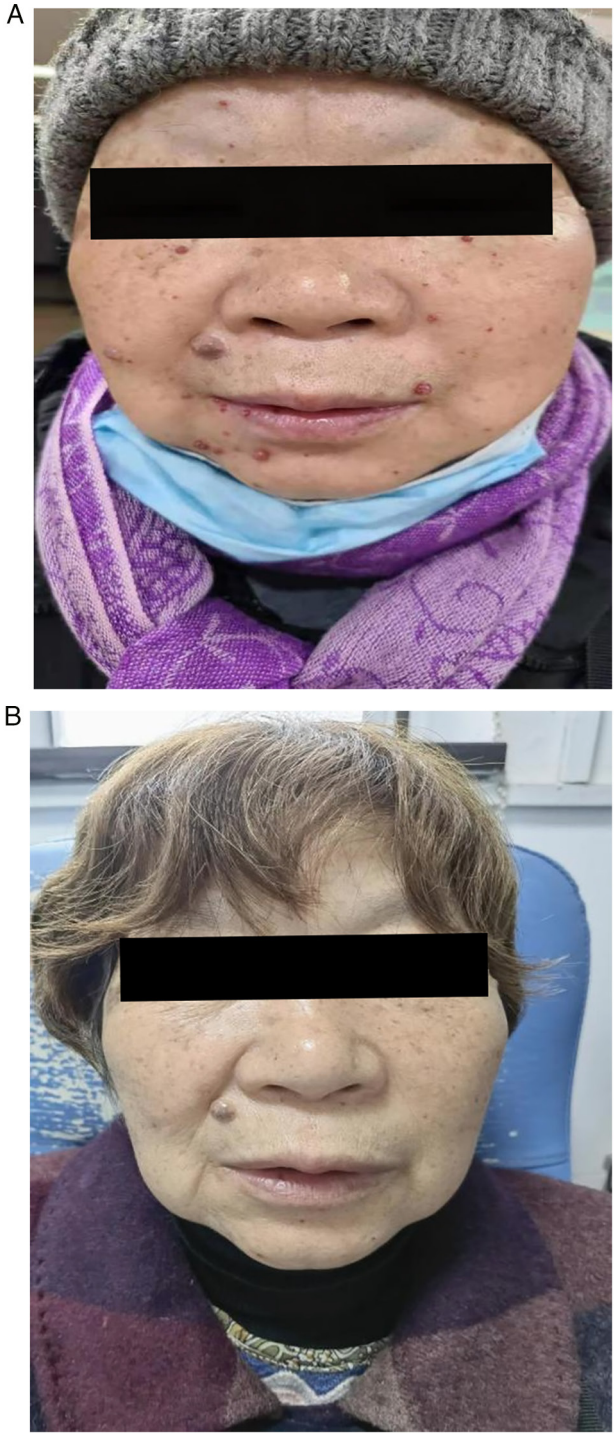

Figure 3. Facial images of the patient. (A) Pearl-like reactive cutaneous capillary endothelial proliferation appearance on the face after one month of camrelizumab treatment. (B) Reactive cutaneous capillary endothelial proliferation disappeared after one month of single-agent thalidomide.

Song *et al* (12) reported that thalidomide may prevent camrelizumab-induced RCCEP. The use of anti-angiogenic drugs for RCCEP prevention remains controversial. At the same time, anti-angiogenic drugs should not be routinely used for RCCEP prevention, as they may increase the burden on the patient and side effects. Consequently, the use of expensive anti-angiogenic drugs in the treatment of RCCEP may not be reasonable. At present, a non-invasive and inexpensive drug therapy is urgently needed to effectively treat RCCEP. Therefore, it is posited that thalidomide may be used to treat RCCEP. In the present study, it was also found that RCCEP nodules shrank in size and decreased in number after thalidomide treatment, and this evidence suggests that blocking angiogenesis is an important mechanism for RCCEP treatment. In addition, the surfaces of the nodules became hard and dark after treatment, indicating reduced hemorrhage; this may indicate that thalidomide helped ameliorate the abnormal activity of immune cells against the epidermis and dermis and ultimately reduced dermal fibrous tissue hyperplasia (31).

In conclusion, low-dose thalidomide monotherapy had excellent efficacy against RCCEP; the possible mechanism of its action appears to be angiogenesis blockade and immune regulation. Preclinical and clinical studies should

be developed to further explore the mechanism, efficacy and appropriate dose of thalidomide when treating patients with RCCEP.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Authors' contributions

SW conceived and designed the present study. SW and CW wrote the original draft. KL and YJ performed the analysis and interpretation of data. ZJ provided administrative, technical and material support, prepared the figures and edited the manuscript. All authors have read and approved the final manuscript. CW and KL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study on a human participant was approved by the Medical Ethics Committee of the Second People's Hospital of Yibin (Yibin, China; approval no. 2021-037-01).

Patient consent for publication

The patient provided written informed consent for the publication of the study and the associated images.

Competing interests

The authors declare that they have no competing interests.

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