

A Case of Capri-Ruzumab-induced Telangiectasia in the Treatment of Liver Cancer and the Research Progress of Traditional Chinese and Western Medicine

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Abstract: *Reactive capillary hyperplasia is a cutaneous toxicity-related adverse reaction caused by immunotherapy with PD-L1 immune checkpoint inhibitors in cancer patients. Compared to other immune checkpoint inhibitors, Carililuzumab has a higher incidence rate. This article aims to share the medical records of a liver cancer patient who developed reactive capillary hyperplasia caused by Carililuzumab. Additionally, it conducts a literature analysis on the research progress of treating capillary hyperplasia with traditional Chinese and Western medicine, to enhance clinicians' understanding of the adverse reactions associated with this drug and expand treatment options for these adverse reactions.*

Keywords: Liver cancer, Camrelizumab, Capillary proliferation, Cutaneous toxicity, Immunotherapy.

1. Medical History Summary

The patient is a 48-year-old male with a history of chronic hepatitis B for over 20 years. He received antiviral treatment with entecavir orally. In February 2022, he experienced upper abdominal discomfort without any apparent cause. He underwent gastroscopy in another hospital and no significant abnormalities were found, so no further treatment was given. In April 2022, he developed jaundice over his entire body. An MRCP examination revealed the following: 1) High-level biliary obstruction, multiple intrahepatic lesions, most likely tumorous changes. 2) Liver cancer with intrahepatic metastasis, lymphadenopathy in the hepatic hilum, and possible compression of the common bile duct. 3) Multiple lymphadenopathy in the abdominal cavity and retroperitoneum. 4) Bilateral renal cysts. In April 2022, he underwent liver biopsy, and the pathology showed moderately differentiated hepatocellular carcinoma. Immunohistochemistry: GS6 (+), CK19 (-), CK20 (-), CK7 (weak +), Glypican-3 (+), KI-67 (20%). He then received six cycles of EOX chemotherapy and oral sorafenib targeted therapy on April 22nd, June 2nd, July 1st, August 2nd, September 2nd, and October 13th, 2022, respectively. During the treatment, he experienced grade I gastrointestinal reactions and grade II-III bone marrow suppression, which improved after symptomatic treatment. In 2023, he received 18 sessions of local liver radiotherapy (specific dose unknown), followed by continuous oral sorafenib targeted therapy. On August 14, 2023, the patient came to our department for a follow-up examination, which indicated tumor progression. Subsequently, on August 17, 2023, September 11, 2023, October 18, 2023, and January 15, 2024, the patient underwent hepatic artery intervention and chemotherapy drug infusion (chemotherapy regimen: epirubicin 20mg + fluorouracil 1.5g + oxaliplatin 120mg). After evaluation, the patient's condition progressed, and on October 8, 2024, October 30, 2024, and December 3, 2024, the patient underwent hepatic artery intervention and

chemotherapy drug infusion (chemotherapy regimen: oxaliplatin 100mg + calcium folinate 0.3g + fluorouracil 0.5g) combined with anti-tumor treatment with 200mg of Carfilzomib. The procedure went smoothly, and the patient did not report any special discomfort.

2. Diagnosis and Treatment Process

After three cycles of using Carililuzumab, the patient developed a vascular mole on the neck (Figure 1), which was of varying sizes, with the largest one measuring approximately 12-15mm in diameter. It protruded from the skin surface and was bright red, without itching, pain, or other special discomfort. It was considered to be a skin reactive capillary proliferation caused by Carililuzumab. Skin examination; hemangioma? Considering the patient's significant adverse reactions, the use of immunotherapy was stopped, and the patient was advised to pay attention to skin protection and avoid scratching and bleeding. If there was accidental damage or bleeding from the hemangioma, Yunnan Baiyao could be applied to the surface and pressed with gauze for 5-10 minutes until no bleeding occurred. During the follow-up visit two months later, new lesions significantly decreased and spontaneously ruptured, scabbed, and fell off, with symptoms significantly alleviated.



Figure 1: Scattered pearl-like vascular nevi on the neck

3. Analysis of Adverse Reaction Correlation

The patient was diagnosed with moderately differentiated hepatocellular carcinoma, with multiple metastases in the liver and lymph nodes. Common metastatic sites of liver cancer include the liver, lungs, lymph nodes, bones, and adrenal glands, with rare metastasis to the brain and peritoneum, and almost no skin metastasis. The patient denied any history of drug allergies. Based on the patient's clinical presentation, it was considered that the skin adverse reaction was caused by drug effects. Referring to the national drug-related adverse reaction evaluation method [1]: (1) The patient developed RCCEP after one cycle of immunotherapy with Cariluzumab, and the patient had no history of drug allergies or related skin diseases. (2) The Cariluzumab instructions and related literature have clearly stated that the drug can cause RCCEP. (3) Symptoms significantly improved after drug withdrawal. (4) Exclusion of related diseases and possible RCCEP caused by concomitant medications. The correlation between RCCEP and Cariluzumab was assessed as highly likely.

4. Modern medical understanding of RCCEP

4.1 Main Clinical Characteristics and Grading Criteria of RCCEP

According to the global cancer data released by the International Agency for Research on Cancer (IARC) on December 15, 2020, the estimated number of new cancer cases worldwide in 2020 reached 19.3 million, and the estimated number of deaths reached 10 million. Among these cases, one in eight males and one in ten females succumbed to cancer. The estimated number of people surviving for five years after being diagnosed with cancer is 50.6 million. By 2040, the number of new cancer cases is projected to reach 28.4 million, representing an increase of nearly 47% compared to 2020. One of the indicators of a country's socioeconomic transformation level is the Human Development Index (HDI). Countries with a low HDI are expected to experience a 95% increase in cancer incidence rate by 2040 compared to 2020, while countries with a medium HDI will see a 64% increase. Furthermore, most of these low or medium HDI countries are undergoing significant growth [2]. With the development of anti-tumor drugs, immunotherapy has gradually gained the same status as traditional chemotherapy. Immune checkpoint inhibitors (ICIs), as a novel immunotherapy approach are primarily divided into programmed death factor-1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). They are widely used in the

treatment of various cancers in clinical practice and have achieved good efficacy. Immunotherapy mainly restores the body's immune defense function against tumor cells by regulating the main immune pathways of the body [3]. However, along with the disruption of the body's immune homeostasis, various immune-related adverse reactions also occur, mainly in the skin system, blood system, endocrine system, digestive system, and urinary system. Among them, skin system adverse reactions are the most common and are among the few that can be managed and even cured without drug discontinuation. Cariluzumab is a human immunoglobulin monoclonal antibody immune inhibitor independently developed in China and was approved for marketing on May 29, 2019 [4]. With its widespread clinical application, adverse reactions have gradually accumulated. Its specific adverse reactions mainly include mucocutaneous toxicity (incidence rate of about 77.1%), endocrine toxicity (incidence rate of about 16.7%), and neuromuscular toxicity (incidence rate of about 0.1% to 0.01%) [5]. Among them, mucocutaneous toxicity is the most significant adverse reaction, with reactive cutaneous capillary endothelial proliferation (RCCEP) being the most prominent. Related studies have shown [6] that cariluzumab has a higher incidence rate of grade 1-2 RCCEP compared to other immune checkpoint inhibitors, and the occurrence of RCCEP is not correlated with age, gender, smoking history, or tumor type [7]. The clinical manifestations of RCCEP are commonly observed on the body surface, with the head, face, and trunk being more common. According to morphology, it is mainly divided into five types: red mole type, pearl type, patch type, mulberry type, and tumor-like type. The diameter is generally 2-10mm, but a single patient can present with multiple morphological types. The color is mostly bright red or dark red, prone to rupture and bleeding. After repeated bleeding, the texture tends to become hard, greatly reducing the risk of bleeding and only affecting the patient's skin appearance. In this case, the main types are pearl-shaped and red mole-shaped, with a bright red color. According to relevant literature [8], the average time from the appearance to the end of RCCEP is 221 days. Most nodules stop growing after 3 to 4 months of initial medication, and some nodules gradually turn black, shrink, dry, or form a pedicle, and finally fall off without leaving obvious scars. Some nodules appear after 3 to 4 months of medication, with smaller shape and darker color [9]. Currently, the main authoritative grading standards for RCCEP are the 2020 Expert Consensus on the Diagnosis and Treatment of Reactive Cutaneous Capillary Hyperplasia Induced by Cariluzumab (Table 1) and the 2024 Chinese Expert Consensus on the Diagnosis and Treatment of Skin Adverse Reactions Related to Immune Checkpoint Inhibitors (Table 2).

Table 1: Grading Criteria for Reactive Capillary Hyperplasia

classification	description	Management Suggestions
G1	The single largest diameter is ≤ 10 mm, with or without ulceration and bleeding	Continue to use medication, and protect the easily rubbed areas with gauze to avoid bleeding. For those who have bleeding ulcers, local compression can be used to stop the bleeding. Continue to use the medication, and protect the easily rubbed areas with gauze to avoid bleeding.
G2	The single largest diameter is greater than 10mm, with or without ulceration and bleeding	Patients with bleeding ulcers can be treated with local compression to stop bleeding, or with local treatment measures such as laser or surgical resection to avoid infection at the ulcer site.
G3	It is generalized and can be complicated by skin infections, which may require hospitalization	Discontinue medication temporarily, and resume administration after recovery to grade ≤ 1 . Use gauze to protect areas prone to friction to prevent bleeding. For patients experiencing ulceration and bleeding, apply local compression to stop bleeding, or adopt local treatment measures such as laser therapy or surgical resection. Complicated infections may also occur
G4	Multiple or generalized, posing a threat to life	Permanent discontinuation of medication
G5	cause death	

Notes: Expert Consensus on the Diagnosis and Treatment of Reactive Cutaneous Capillary Hyperplasia Induced by Cariluzumab in 2020.

Table 2: Grading criteria for reactive capillary proliferation

classification	standard
G1	Multiple or solitary nodules, with the largest nodule having a diameter of ≤ 10 mm, accompanied by or not accompanied by ulceration and bleeding.
G2	Multiple or solitary nodules, with the largest nodule having a diameter > 10 mm, with or without ulceration and bleeding.
G3	Extensive skin nodules, secondary to skin infection.
G4	Multiple and widespread, posing a threat to life.
G5	result in death

Notes: Chinese Expert Consensus on Diagnosis and Treatment of Skin Adverse Reactions Related to Immune Checkpoint Inhibitors in 2024.

4.2 The Main Pathogenesis of RCCEP

Currently, there is no definitive conclusion on the pathogenesis of RCCEP. It is speculated that there may be a close relationship between immune mechanisms and angiogenesis. Tissue biopsy of RCCEP can clearly show that the arrangement of capillaries in the lesion area is sparser compared to normal blood vessels, accompanied by thickening of the endothelial layer and visible red blood cells in the lumen. The interstitial tissue mainly presents a fibrotic state. Microscopic immunostaining can observe that CD4+ cells are mainly surrounding the capillaries, accompanied by IL-4-induced M2 macrophages (CD163+) scattered around, promoting vascular proliferation by releasing vascular endothelial growth factor. Relevant literature suggests that the occurrence of RCCEP is mainly due to PD-1 blocking the specific immune suppression pathway of the body, which reactively activates the immune response of the body, breaking the balance between promoting and inhibiting vascular growth factors, thereby stimulating the secretion of interleukin-4 (IL-4) and macrophage colony-stimulating factor (M-CSF) by T helper 2 cells (Th2), promoting the differentiation and expansion of resident M0 macrophages in the skin to M2 type, and releasing vascular endothelial growth factor A (VEGF-A), stimulating benign proliferation of skin capillary endothelial cells [10]. There are also relevant literature indicating that carililuzumab can bind to VEGFR-2 to promote the occurrence of hemangiomas. RCCEP is more common in the epidermis, with a very low incidence in internal organs [11]. Since the epidermis of the human body is similar to the thymus in immunology, the main lymphocytes of the skin immune system are T cells, which have a pro-epidermal nature, with more than 90% localized around the dermal blood vessels of the skin. Due to the removal of immune suppression by carililuzumab, it is more likely to cause skin immune reactions [12]. Some researchers believe [13] that the occurrence of RCCEP is closely related to hypoxic environment. Carililuzumab relieves the body's immune suppression state, leading to the proliferation and infiltration of a large number of immune cells, and a large amount of oxygen is consumed, forming a hypoxic state, which is prone to form immune inflammatory reactions. [14] At the same time, under hypoxic conditions, VEGF will greatly stimulate the induction of endothelial cell proliferation [15]. However, there is a certain dependence on the patient's own VEGF content. Related research shows that the content of VEGF is positively correlated with the incidence of RCCEP. Zhang Liqin et al. [16]. howed a positive correlation between VEGF and carililuzumab-induced RCCEP in their study, and the predictive sensitivity reached 80.4%, with a specificity of 83.3%, providing a basis for the prediction of RCCEP. At the same time, related research also shows [17] that the early occurrence time of RCCEP is positively correlated with drug dose.

5. Treatment Measures for RCCEP

5.1 Non-pharmacological Therapy

Before using Carilizumab for treatment, it is necessary to have in-depth communication with the patient and their family to inform them of the main adverse reactions, so that the patient can be mentally prepared. After the occurrence of RCCEP, timely psychological counseling should be provided to the patient, informing them of the main causes and common clinical manifestations, and clearly informing them of the RCCEP. Most of them are self-limiting diseases, which usually subside on their own after 1-2 months of using Carilizumab and are non-infectious [18]. This can improve patients' psychological confidence, guide them in treatment, and inform them to pay attention to skin care, avoid scratching the hemangioma site, and prevent bleeding and infection. For friction-prone areas such as the head and neck, hands, etc., band-aids or gauze should be applied. If bleeding occurs accidentally, cotton swabs or a small amount of Yunnan Baiyao or thrombin freeze-dried powder can be used to press for 3-5 minutes until the bleeding stops [19]. If necessary, laser resection can also be used. There are also related studies [20] indicating that aseptic thread ligation has a certain therapeutic effect on the treatment of this disease and the reduction of complications.

5.2 Pharmacotherapy

For RCCEP caused by camrelizumab, most cases are of G1-G2 grade, and most do not require treatment discontinuation. RCCEP is not sensitive to glucocorticoids. Related research shows [21] that the efficacy rate of apatinib in treating RCCEP caused by camrelizumab can reach up to 50%. Wang Qin et al. [22] conducted a safety analysis on 102 cases using camrelizumab, indicating that the incidence rate of RCCEP in the 52 cases treated with a combination of anti-angiogenic drugs was 13.46%, while the incidence rate in the non-anti-angiogenic drug combination group was 56%, suggesting that combining camrelizumab with anti-angiogenic drugs can significantly reduce the incidence rate of RCCEP. Wang Feng et al. [23] conducted a study on the treatment of primary liver cancer using camrelizumab and camrelizumab combined with apatinib in different groups. The results showed that the incidence rates of RCCEP in the two groups were 77.1% and 33.3%, respectively, indicating that apatinib can significantly reduce the incidence rate of RCCEP. Yin Nannan et al. [24] showed that camrelizumab combined with anlotinib can reduce the incidence rate of RCCEP and induce remission. Among 136 patients, 79 (58.09%) developed RCHs, including 31 (42.47%) in the observation group and 48 (76.19%) in the control group. The incidence rate of RCHs in the observation group was significantly lower than that in the control group, with a statistically significant difference ($P < 0.001$). Professor Zhang

Yiqin [25] observed the incidence rate of RCCEP when using different anti-angiogenic drugs in combination with camrelizumab. The research results showed that the incidence rate was 83.3% for bevacizumab, 68.2% for anlotinib, 43.8% for fructinib, 64.7% for regorafenib, and 14.0% for apatinib. The results indicated that different anti-angiogenic drugs could reduce the incidence rate to varying degrees, but the incidence rate was lowest with apatinib. There are also related studies [26] showing that thalidomide has a certain effect in inhibiting VEGF, and camrelizumab combined with thalidomide can reduce the incidence rate of RCCEP. Song Geng and Zhang Meiyan [27][28] found in their study on the prevention of RCCEP with thalidomide that the experimental group (thalidomide combined with cabergolide) significantly outperformed the control group (cabergolide alone) in terms of incidence and symptom relief. This suggests that thalidomide does have a certain effect on the prevention and treatment of RCCEP. For most patients with G 1-G2 degrees, treatment is generally not recommended. If necessary, topical super-potent steroids can be used. For multiple cases, oral thalidomide can be taken, and antibiotic ointment can be used for anti-infection treatment if necessary. If the hemangioma is large, surgery, laser, liquid nitrogen freezing, and other treatments can be used. Patients with \geq G3 should consider suspending treatment until they recover to G 1-G2 before resuming medication treatment [29]. However, relevant clinical studies have shown that [30] RCCEP is more likely to occur in the treatment of elderly patients with advanced esophageal cancer using durvalumab combined with chemotherapy, but its severity is not severe enough to warrant discontinuation of treatment. This provides some reference for the development of future clinical treatment plans for esophageal cancer.

6. Traditional Chinese Medicine's Understanding of RCCEP

6.1 Etiology and Pathogenesis of PCCEP

Traditional Chinese Medicine (TCM) does not have a specific term for RCCEP, but it can be classified under the categories of "drug rash", "drug toxic rash", "blood disease", and "blood tumor". In the Tang Dynasty, Wang Tao first proposed the term "blood tumor" in his work [31], describing it as "swelling that is soft and tender, similar to a blood tumor. If it is soft and tender, it indicates the presence of blood. If there is a protrusion in the skin and flesh, initially resembling a plum, and gradually grows larger, without itching or pain, and is not firm, but soft when pressed, it is a blood tumor." Chen Yan's "Three Causes and One Disease Syndrome" divides tumors into five types and six types of growths, mentioning "those with red veins interconnected are called blood tumors". There is no consensus on the etiology and pathogenesis of RCCEP. Some scholars believe [32] that the main cause is internal deficiency and external pathogenic factors. Due to the physical weakness of tumor patients and the use of anti-tumor drugs, their internal environment becomes unstable and external environment weakens. Pathogenic factors invade the body surface, and drug toxicity takes advantage of this weakness, combined with external toxins diffusing from the skin and hair, leading to the disease. Other scholars [33] believe that the disease is caused by tumor patients' inherent physical weakness and drug toxicity invading the body,

leading to pathogenic factors accumulating and turning into heat, forcing blood to flow abnormally and overflowing the skin surface. At the same time, heat tends to consume qi and damage yin, leading to both qi and yin deficiency. Some scholars [34] approach the diagnosis and treatment from the perspective of defending qi and nourishing yin, providing treatment based on different stages of pathogenic factors, but all ultimately stem from "deficiency of vital energy and weakened body, heat-toxin and yin damage".

In summary, the pathogenesis of RCCEP is mainly due to "deficiency of vital energy", "heat-toxin", and "yin deficiency". It is mainly caused by a weak constitution, internal invasion of medicinal toxins, internal heat transformation, forced blood flow, heat-induced yin damage, and subsequent blood stasis. This leads to the external manifestation of heat-toxin and blood stasis on the skin surface, resulting in the disease.

6.2 Traditional Chinese Medicine for the Treatment of RCCEP

Traditional Chinese medicine has different theories for the treatment of RCCEP. Professor Zheng Xin [35], from the perspective of liver and kidney theory, believes that patients with liver hyperactivity have both blood heat and blood deficiency syndromes, and should be given both heat clearing and liver soothing treatments, as well as nourishing yin and blood. Mild cases can be treated with modified Xianfang Huosheng Drink, while severe cases can be treated with modified Xijiao Dihuang Decoction and Puji Disinfection Drink. Due to kidney deficiency, patients with suppressed fire should be treated with nourishing yin and kidney, as well as promoting blood circulation and removing blood stasis. Kidney Qi Pills and Dihuang Yinzi can be used for treatment. Li Yan et al. [36] compared 96 patients with RCCEP9 induced by Carilizumab with thrombin freeze-dried powder and Shengyu decoction orally. The results showed that the total clinical effective rate of the observation group was 87.5%, significantly higher than the control group's 75.0% ($P < 0.05$). This indicates that Shengyu decoction can significantly alleviate the symptoms of RCCEP, which may be related to regulating the patient's immune function. Zhu Jie et al. [37] believed from the perspective of the dialectical theory of Wei Qi Ying Xue that the main pathogenesis of this disease is the infiltration of immune heat and toxins into the Ying blood, forcing blood to flow recklessly, causing blood heat to damage yin and then removing blood stasis. Treatment should be based on clearing heat and nourishing blood, nourishing yin and removing blood stasis. At the same time, Xijiao Dihuang decoction can be used as the main treatment, and compound purple grass oil can be applied topically. However, due to the lack of large-scale research, its effectiveness still needs further investigation. Wei Wenpei [38] used 62 patients who used Carrelizumab. The experimental group made them take Xiaofeng Powder granules orally. The results showed that the incidence rate of the experimental group was 29.0%, and the incidence rate of the control group was 64.5%, which showed that the incidence rate of RCC EP could be reduced to a certain extent when taking Xiaofeng Powder. At the same time, the incidence rate of RCC EP could also be significantly reduced when Carrelizumab combined with bevacizumab against vascular endothelial growth factor. The results of the

study using Qigui Zicao oil for external treatment showed that the treatment group had a significantly better effect on RCCEP degradation than the control group, and also had a significant improvement in quality of life [39]. Luo Zhenyu et al. [40] found that the experimental group had a significantly higher symptom relief rate than the observation group in the treatment of RCCEP caused by Carilizumab using Diyu Huaihua granules, and could also delay the onset of RCCEP.

7. Conclusion

With the increasing number of cancer patients worldwide, anti-tumor methods are also evolving rapidly. However, with the continuous launch of new drugs, the emergence of adverse reactions has become an urgent problem to be solved, which has also become a major challenge in modern medicine. The most common adverse reaction of Carfilzomib is RCCEP, which is closely related to patient survival and quality of life. When using Carfilzomib in clinical practice, prevention and treatment should be synchronized. Before treatment, actively predict adverse reactions, provide knowledge popularization, actively give symptomatic support during treatment, and give certain anti-RCCEP drugs. After the onset of the disease, actively give different treatment measures according to different grades, such as thrombin freeze-dried powder, Yunnan Baiyao, etc. If necessary, stop treatment and wait for symptoms to alleviate before resuming treatment. If special, surgical treatments such as laser and liquid nitrogen freezing can be used to remove it. At the same time, traditional Chinese medicine has a unique theoretical system. As part of China's traditional cultural treasures, it adopts the overall concept as the guiding ideology, yin and yang and the five elements as the philosophical foundation, the meridians and organs as the physiological and pathological basis, and syndrome differentiation as the clinical treatment characteristic. It has its own theoretical basis for HFS treatment, and the treatment has both the theoretical and practical basis of Chinese culture. Many studies have shown that the combination of traditional Chinese and Western medicine in the treatment of RCCEP has a huge effect on improving patient survival rate and reducing toxicity and enhancing efficacy. More and more researchers have begun to study in the field of integrated traditional Chinese and Western medicine, hoping to find a better solution in the field of immune therapy adverse reactions.

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