Reactive cutaneous capillary endothelial proliferations of the eyelids induced by camrelizumab: A case report

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Received October 10, 2023; Accepted January 5, 2024

DOI: 10.3892/br.2024.1743

Abstract. With the widespread application of immune checkpoint inhibitors, a series of adverse events (AEs) related to treatment resulting from alterations in the immune system have emerged that warrant attention. The present study report the case of a patient with reactive cutaneous capillary endothelial proliferations (RCCEPs) on the eye lid, following treatment with the programmed cell death protein 1 inhibitor camrelizumab (SHR-1210) for stage IIa2 well- to moderately differentiated squamous cell carcinoma of the cervix. Although RCCEPs have been revealed to be the most common AEs of SHR-1210, they are usually distributed on the head, neck, trunk and extremities. The current study presents a rare case of ocular RCCEPs induced by SHR-1210. Prompt diagnosis and treatment of immune-related AEs is crucial for the optimal management of patients. Although RCCEPs are usually slight-risk toxicities that pose no threat to the continuity of treatment, lesions with unusual distributions that cause disturbances in normal life require proper treatment, such as surgical excision.

Introduction

Recently, a growing body of literature has focused on reshaping immunomodulation by blocking the abnormal upregulation of immune checkpoint proteins, including programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), PD-L2 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to prevent tumours from co-opting immune resistance and to enhance antitumour specificity (1). Owing to the introduction to clinical practice of immune checkpoint inhibitors (ICIs), a spectrum of monoclonal antibodies (mAbs) intervening in the interactions of immune checkpoints, high efficacy has been achieved in the treatment of malignant tumours, especially those refractory to conventional therapies, which enriches the therapeutic arsenal (2).

However, clinicians have been confronted with a set of immune-related adverse events (irAEs) upon the use of ICIs, albeit at the same time as promising antitumour activity (2,3). The irAEs caused by ICIs are experienced by 20-85% patients, and can affect almost all organs, with cutaneous irAEs being the most frequent toxicities, affecting 7-68% of patients receiving ICIs, followed by gastrointestinal/hepatic irAEs (7-50%), endocrine irAEs (1-23.7%) and pulmonary irAEs (0-9%) (2,4-6). Other rare irAEs affect systems such as the cardiovascular, neurological, ocular, rheumatological, renal and haematological systems (2). It is worth noting that some irAEs are life threatening, albeit at a relatively low incidence rate. According to a previous meta-analysis, the incidence rates of irAE-associated fatality were 0.36% for PD-1 inhibitors), 0.38% for PD-L1 inhibitors and 1.08% for CTLA-4 inhibitors (7). Within the spectrum of fatal irAEs, myocarditis accounted for the highest fatality rate (39.7-46.0%), albeit at an incidence of 1.14% (7-9). The incidence of all-grade and high-grade ICI-related pneumonitis also increased significantly compared with that of the controls (RR, 4.70 and 3.33, respectively) (10). Other severe irAEs with high fatality rates include hepatitis, myositis, nephritis, and neurological and hematological toxicities (10-17%) (7). The expression of PD-1 has been found on a broad range of immune cells, including T lymphocytes, B lymphocytes, monocytes, macrophages, dendritic cells and natural killer cells, and is upregulated in tumour infiltrating T lymphocytes (1). The binding of PD-1 with ligands (mainly PD-L1) leads to immunotolerance and tumour escape by inhibiting effector T cells and promoting regulatory T cells (1). Monoclonal antibodies (mAbs) intervening in the interactions within PD-1/PD-L1 pathway can augment endogenous antitumour immunoreactions, modulate components in the tumour microenvironment and restore balanced immune homeostasis (1,2). Camrelizumab (SHR-1210) is a humanized high-affinity IgG4 mAb against PD-1 (11,12). Since receiving its first approval in China for relapsed or refractory classical Hodgkin's lymphoma in May 2019, SHR-1210 has shown tremendous efficacy in various cancer types (11,13), including advanced hepatocellular carcinoma (14,15), advanced gastric carcinoma (15), advanced esophageal carcinoma (16) or advanced esophagogastric junction carcinoma (15), metastatic colorectal cancer (17),

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Key words: programmed cell death protein 1, immune checkpoint inhibitors, camrelizumab, immune-related adverse events, reactive cutaneous capillary endothelial proliferations

nasopharyngeal carcinoma (18), advanced osteosarcoma (19), advanced non-squamous non-small cell lung cancer (20), advanced or recurrent cervical cancer (21,22), and advanced triple-negative breast cancer (23). However, SHR-1210 is associated with a unique AE that has a high incidence rate of 67-97%, namely, reactive cutaneous capillary endothelial proliferations (RCCEPs) (24-26). While RCCEPs related to the treatment of SHR-1210 have been widely reported in the head, neck, trunk and extremities according to previous studies (24,27-29), to the best of our knowledge, ocular RCCEPs have not been reported. The present study describes a rare case of ocular RCCEPs and reviews the current methods to alleviate and treat this AE.

Case report

A 44-year-old woman was diagnosed with cervical carcinoma at Peking University First Hospital (Beijing, China) in April 2021. The pathological results revealed stage IIa2 well- to moderately differentiated squamous cell carcinoma of the cervix following a total hysterectomy plus bilateral adnexectomy and pelvic lymphadenectomy. The patient received total three cycles of neoadjuvant chemotherapy with the platinum-doublet chemotherapy (intravenous paclitaxel at a dose of 300 mg and intravenous cisplatin at a dose of 120 mg each time) 1 month before the sugery, 1 week after the sugery and 1 month after the sugery, respectively. After 20 days, the patient began to receive radiotherapy (50 Gy in 25 fractions delivered within 5 weeks). In addition to the traditional neoadjuvant chemotherapy and radiotherapy, the patient underwent an immunohistochemical examination of PD-L1 expression, which showed a combined positive score (CPS) (30,31) of 35. The CPS was used to assess the PD-L1 expression in tumour cells, which was defined as the sum of the total number of PD-L1-postive cells (tumour cells, lymphocytes and macrophages) divided by the total number of tumour cells, multiplied by 100 (30,31). Specimens with CPS of 1 or higher were considered to be PD-L1 postive (30,31). The patient was subsequently treated with 200 mg SHR-1210 intravenous transfusion once every 3 weeks.

The patient developed sporadic dome-shaped or papillary red lesions 1-3 mm in size on the eyelid margin, forehead and scalp, without pruritus or pain, 1 week after the first cycle of SHR-1210. The patient received another injection of 200 mg SHR-1210 20 days later. During this time period, the lesions increased in both size and number. When the patient presented to the Department of Ophthalmology 1 month later, three papillary, smooth, red lesions were present on the lower eyelid and lateral canthus of the right eye, and the lower eyelid of the left eye, with sizes of 1x3, 1x3 and 5x3.5 mm respectively (Fig. 1A-C). There were domed, smooth, red sporadic lesions on the forehead (Fig. 1D and E). The patient complained of eye irritation and foreign body sensation. Several lesions on the scalp were associated with ulceration, bleeding and pigment deposition (Fig. 1F). No obvious abnormalities, except lesions, were observed in terms of visual acuity, intraocular pressure, anterior segment under slit lamp, optical coherence tomography angiography (Fig. S1) and fundus photography. The lesions on the eyelid margin were successfully resected (Fig. 2A and B). Histological analysis of the ocular lesions showed a dense proliferation of briskly growing fusiform and ovoid cells, forming several spaces, which is a typical feature for RCCEPs (Fig. 2C-E). The patient has not received SHR-1210 therapy since then, as all the antitumour treatments for the patient had been successfully completed. The other RCCEPs on the scalp and forehead disappeared ~5 months from the occurrence, which is consistent with the spontaneous regression median time of 221 days (range, 14-448 days) for this condition (24). No recurrence of RCCEPs was found during the 1-week, 6-month and 1-year follow-up examinations in the Department of Ophthalmology (Fig. 2F and G). The patient undergoes regular check-ups at the Department of Obstetrics and Gynecology every 2-3 months and has received imageological examinations regularly, which have shown a good prognosis without recurrence.

Methods

Immunohistochemistry. Immunohistochemistry was performed using formalin-fixed paraffin-embedded specimens. The lesions were fixed with 10% neutral buffered formalin (room temperature for 24 h), dehydrated with an alcohol gradient, infiltrated and embedded in paraffin. Sections were cut to a 4-μm thickness. After incubating with 3% bovine serum albumin for 1 h at room temperature, the sections were stained with anti-PD-L1 rabbit monoclonal primary antibody (dilution 1:200; clone SP263 cat. no. 741-4905/07419821001; Roche Tissue Diagnostics) at 4˚C overnight. The sections were washed and covered with enzyme conjugated goat anti-rabbit IgG (ready-to-use; cat. no. PV6001; Origene Technologies, Inc.) for 1 h at room temperature, followed by visualization with a diaminobenzidine kit (cat. no. ZLI-9017; Origene Technologies, Inc.). The stained sections were evaluated by light microscopy (Olympus BX41; Olympus Corporation).

Histology. The formalin-fixed paraffin-embedded specimens were created from resected lesions that were immediately fixed with 10% neutral buffered formalin (room temperature for 24 h), dehydrated with an alcohol gradient, infiltrated and embedded in paraffin. Sections were cut to a 4-μm thickness, dewaxed, and stained in hematoxylin for 3 min (room temperature) and in eosin for 3 min (room temperature). The stained sections were evaluated by light microscopy (Olympus BX41).

Discussion

SHR-1210 is a humanized high affinity anti-PD-1 IgG4 mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (11,12); it received its first approval in China in May 2019 for relapsed or refractory classical Hodgkin's lymphoma, and has received approval for a number of other tumours since then (11).

Although they have promising antitumour activity, ICIs have a wide spectrum of irAEs involving almost all organ systems, with the dermatological AEs (DAEs) being the most common toxicities (3). However, the AEs of SHR-1210 are of different types than other ICIs such as pembrolizumab and nivolumab, for which rash, pruritus and vitiligo are the most frequently reported DAEs (3,32), while SHR-1210 has unique RCCEPs (24). Previous clinical trials revealed that treatment-related AEs occurred in 83.3-97.2% of patients receiving

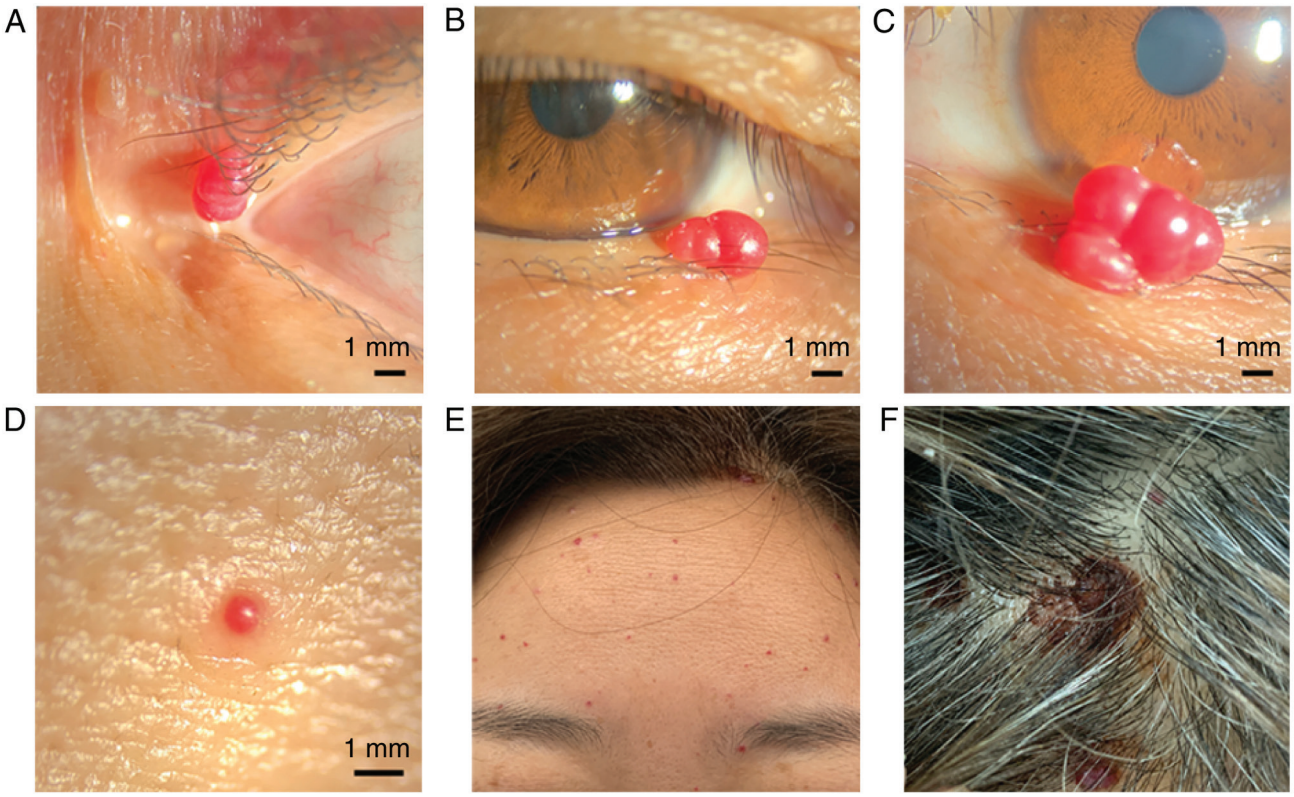

Figure 1. Morphology of the RCCEPs. (A) A papillary, smooth, red lesion located on the lateral canthus of the right eye, measuring 1x3 mm. (B) Another papillary, smooth, red lesion located on the lower eyelid of the right eye, measuring 1x3 mm. (C) A papillary, smooth, red lesion on the lower eyelid of the left eye, measuring 5x3.5 mm. (D) A domed, smooth, red lesion located on the forehead, measuring <1 mm. (E) Domed, smooth, red sporadic lesions distributed on the forehead. (F) A lesion on the scalp that exhibited ulceration, bleeding and pigment deposition [(A-C) x10 magnification; (D) x16 magnification].

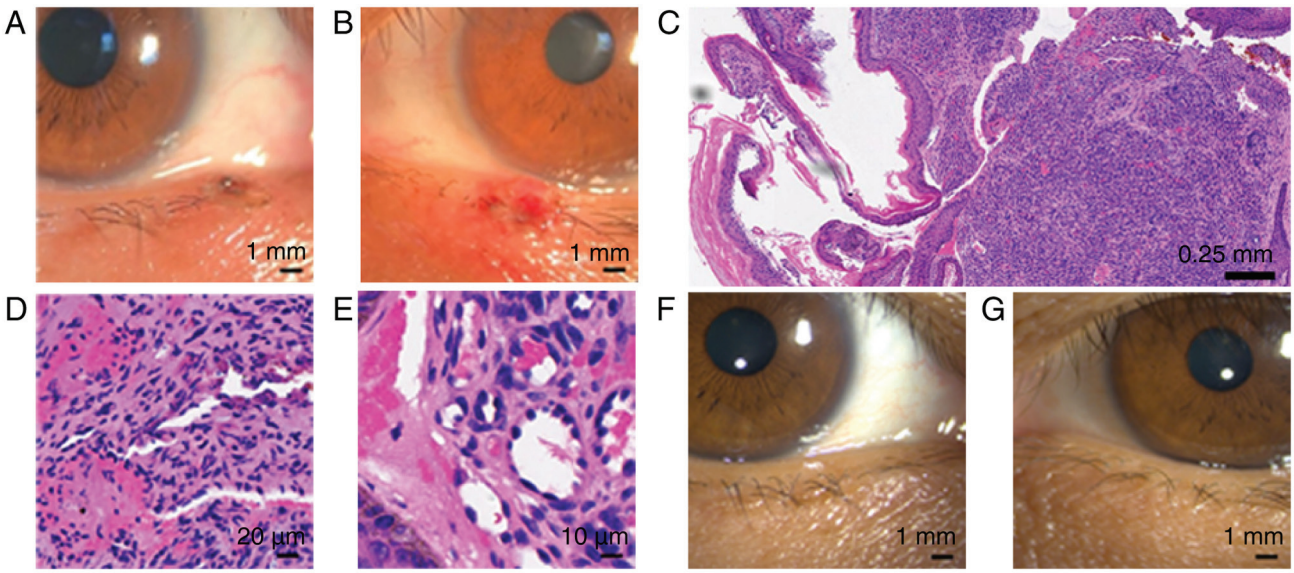

Figure 2. Histological manifestation and prognosis of the RCCEPs. (A) The lower eyelid of the right eye at 1 week after excision, showing wound healing without bleeding. (B) The lower eyelid of the left eye at 1 week after excision, showing wound healing without bleeding. (C-E) The histological manifestation of RCCEPs in this patient, using hematoxylin and eosin staining with different magnifications, which showed dense proliferation of briskly growing fusiform and ovoid cells, forming several spaces [(C) x2, (D) x20 and (E) x40 magnification]. (F) The appearance of the lower eyelid of the right eye without RCCEP recurrence at 1 year after excision. (G) The appearance of the lower eyelid of the left eye without RCCEP recurrence at 1 year after excision [(A, B, F and G) x10 magnification].

treatment with SHR-1210 (11,12,25). Although dermatological toxicities still account for most AEs after SHR-1210 treatment, RCCEPs seem to be novel DAEs absent in other ICIs and are the most common AEs of SHR-1210 (24,25). In a phase I clinical study of SHR-1210, Chen *et al* (24) systematically enrolled 98 patients with advanced solid tumours to examine DAEs

after treatment with SHR-1210, and observed that RCCEPs occurred most frequently on cutaneous/mucosal surfaces (85.7% of patients), followed by rash (29.6%) and pruritus (16.3%). Mo *et al* (12) enrolled 36 patients with advanced solid tumours to assess the safety of SHR-1210 and found that RCCEPs (83.3%), pruritus (33.3%) and fatigue (30.6%) were the top three treatment-related AEs. Another phase I clinical trial of SHR-1210 in patients with advanced oesophageal squamous cell carcinoma revealed that the occurrence of RCCEPs was 76.7% (25).

The onset time of RCCEPs after the initial use of SHR-1210 was dose-dependent, with a median time of 20 days for all doses and a median time of 18.5 days for the 200 mg dose (24). In the case of the present patient, the onset time of RCCEPs was 7 days with a dose of 200 mg. According to a previous clinical trial, the RCCEPs were found as multiple, diffuse red papules or macules with clear boundaries, which gradually enlarged during treatment, accompanied by recurrent haemorrhage without pain or pruritus, and mostly regressed spontaneously with a median time of 211 days (24). Although RCCEPs are widely distributed over the skin and mucosa, the head and neck, trunk and extremities are the most commonly affected areas, with the mucosa, sclera, gingiva, nasal cavity, buccal mucosa, lip and tongue reported in a few cases (24,27,33,34). Although RCCEPs are usually small lesions with a maximum diameter of 2 mm, as reported by previous clinical trials (24,29), one case report showed that a RCCEP located on the inner thigh in a patient with esophageal squamous cell carcinoma treated with SHR-1210 was ~40 mm (24), and another case report showed that an oral RCCEP on the gingiva in a patient with non-small cell lung cancer treated with SHR-1210 was 15x7 mm (33). To the best of our knowledge, no cases of ocular RCCEPs have been reported in previous studies. Based on the pathogenesis of RCCEPs, it is feasible for these lesions to grow in the eye region but with low incidence.

In the present case, the RCCEPs occurred at the junctional margin of the skin and mucosa. However, an examination of the palpebral conjunctiva, bulbar conjunctiva and retinal vessels (Fig. S1) showed no vascular-related abnormalities. Therefore, we hypothesized that the occurrence of RCCEPs is mostly associated with the vascular network in epithelial tissue. As an emerging phenomenon, there is little experience with the treatment of RCCEPs in the eye. Based on our previous experience of the treatment of RCCEPs, resections of the RCCEPs were chosen for the protruding palpebral lesions. The follow-up observations at 1 year post-resection showed no recurrence or lasting visual signs of the lesions.

Although the precise mechanism of SHR-1210-related RCCEPs remains unclear, it has been found that SHR-1210 may mediate activation of vascular endothelial cells through binding to vascular endothelial growth factor receptor 2 (VEGFR2) (35). Under most circumstances, RCCEPs will regress spontaneously after SHR-1210 treatment, with a median time of 211 days (24). However, prompt treatment of RCCEPs is sitll required in some cases, including those with a high risk of haemorrhage (plump or vulnerable lesions) (24), when there is difficulty in distinguishing a metastatic tumour from an RCCEP (36) or in cases with obvious clinical manifestations, such as the eye irritation in this patient. The treatments for RCCEPs are predominantly focused on two aspects: Medication and surgery.

Since the pathogenesis of RCCEPs has links with the upregulation of the VEGF signalling pathway, finding the antiangiogenesis target among the VEGF/VEGFRs is a promising prospect. Apatinib, a novel anti-angiogenic molecule, is a selective VEGFR2 tyrosine kinase inhibitor that can inhibit angiogenesis, as well as induce autophagy and apoptosis of tumour cells (37). A new spectrum of seminal studies has demonstrated that the combination of ICIs and antiangiogenic agents could improve efficacies and reduce toxicities (15,26,28,38). The combination of SHR-1210 with apatinib exhibited synergistic activities, with sensitive antitumour activity and manageable safety profiles (14,15,26,38). In clinical studies of SHR-1210 plus apatinib in solid tumours, the incidence of RCCEP ranged from 11.9-29.5% (14,15,26), which was significantly lower than the occurrence rate of 67-97% for SHR-1210 monotherapy (24-26). Significant regression of RCCEPs was reported in several cases after the initiation of apatinib (36,39). Furthermore, unlike other antiangiogenesis agents such as bevacizumab, which can increase anastomotic leakage and wound healing complications, apatinib is free of this problem (38). Taken together, the feasibility of the combination therapy of apatinib plus SHR-1210 to reduce prevalent irAEs such as RCCEPs and to improve efficacy deserves deeper interrogation, in order to guide further clinical practices. Curative surgical resection is another optional therapy. In some conditions, it is difficult to differentiate the tomour-like RCCEPs from suspect metastatic lesions, which increases the demands of lesion excision to obtain definitive pathological findings to avoid delaying antitumour treatment (36). Other surgical indications include lesions with an unusual distribution, such as in the present case where the appearance and normal blinking were affected, as well as in lesions with a high risk of bleeding. The present case highlights the significance of the prompt diagnosis and treatment of irAEs. Although RCCEPs are usually slight-risk toxicities that pose no threat to the continuity of treatment, lesions with distributions that cause disturbances in normal life require proper treatment, such as surgical excision.

Acknowledgements

Not applicable.

Funding

The study was supported by National High Level Hospital Clinical Research Funding: Interdepartmental Clinical Research Project of Peking University First Hospital (grant no. 2022CR24).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

XZ, XY and YW all provided care to the patient, advised on patient treatment and analyzed patient results. XZ drafted the

manuscript. XY was responsible for study conceptualization and supervision. YW performed critical revision of manuscript. All authors approved the final version of this manuscript. YW is responsible for the overall content as guarantor. XZ, XY and YW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The requirement for approval was waived by the institutional review board owing to the anonymized and retrospective nature of the report.

Consent for publication

Written informed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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