LETTER TO THE EDITOR

Reactive capillary hemangiomas induced by camrelizumab (SHR-1210), an anti-PD-1 agent

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We report herein two cases of reactive capillary hemangiomas during the clinical trials of SHR-1210, a humanized anti-PD-1 IgG4 antibody.

Case 1

A female in her 20s with a history of stage IVa Hodgkin's lymphoma was enrolled in a phase I/II trial (NCT03250962) for a humanized anti-PD-1 IgG4 antibody camrelizumab (SHR-1210). One month after the first SHR-1210 injection, she developed several, 2-5 mm in size, dome-shaped, bright red papules on her scalp, face, chest, abdomen, and extremities (Figure 1(A)). SHR-1210 therapy was continued, and the lesions gradually increased in size and in number over the subsequent three months. One lesion on the right temporal scalp rapidly developed into a 20 x 15 mm, red, friable, sessile nodule with associated ulceration and bleeding. Histological examination of the nodular lesion showed numerous vascular spaces lined by endothelial cells, surrounded by fibromyxoid stroma and scattered inflammatory cells (Figure 2). The histology of this lesion combined with its clinical appearance was typical for pyogenic granuloma. The histological manifestation of the papule lesion on the forehead is consistent with cherry angioma, formed by dilated vascular channels filled with erythrocytes. Immunohistochemical studies revealed positive staining for the surface markers factor VIII-related antigen (von Willebrand factor, vWF), CD31, and CD34, negative stains to lymphoid markers and EBV with low Ki67.

Case 2

A female in her 70s with a history of stage IV lung adenocarcinoma who was receiving injections of SHR-1210 in a phase II trial (NCT03085069) developed similar findings. Two weeks after the first injection, she developed multiple, 2-5 mm, dome-shaped, bright red papules on her scalp, face, neck, chest, abdomen, and back (Figure 1(B)). The patient remained on SHR-1210 and the lesions increased in both size and number. Histological examination of one lesion from the face revealed dilated vascular channels filled with erythrocytes, located on the upper-mid-dermis, lined by endothelial cells. Based on these clinical and histopathological findings, a diagnosis of eruptive cherry angiomas was made.

Discussion

Reactive capillary hemangiomas are characterized by rapid capillary proliferation associated with etiologic factors such as trauma, infection and medications. They are a group of benign vascular tumors including papillary endothelial hyperplasia, bacillary angiomatosis, epithelioid hemangioma, glomeruloid hemangioma, eruptive cherry angiomas, pyogenic granuloma and among others [1]. The main concern in these cases is secondary malignant vascular tumors in relation to the known malignancy and/or treatment. However, the clinical and histologic features observed in these cases make the possibility of vascular malignancy highly unlikely.

The clinical presentation and onset of lesions in both cases suggest a temporal relationship between SHR-1210 administration and the development of reactive capillary hemangiomas. The patient in ***case 1*** developed two types of reactive capillary hemangiomas, i.e. pyogenic granuloma and cherry angioma. However, the predominant lesions were noted to be cherry angiomas and the development of a pyogenic granuloma may be secondary to trauma. Eruptive cherry angiomas is a rare phenomenon that has been reported following exposure to nitrogen mustard, VEGF-inhibitors, cyclosporine, and in association with HHV-8 and lymphoproliferative disorders [2–5]. The outcome of three clinical trials on SHR-1210 has revealed the notably high incidence of reactive capillary hemangioma as a common adverse reaction [6]. As stated by Fang et al., 88% of subjects in the trial with SHR-1210 alone on nasopharyngeal carcinoma developed reactive capillary hemangiomas and were self-resolved during the treatment. However, in the combination trial with gemcitabine plus cisplatin, only 22% of the subjects developed reactive capillary hemangiomas [7]. Additionally, in the study on fixed-dose SHR-1210 by Mo

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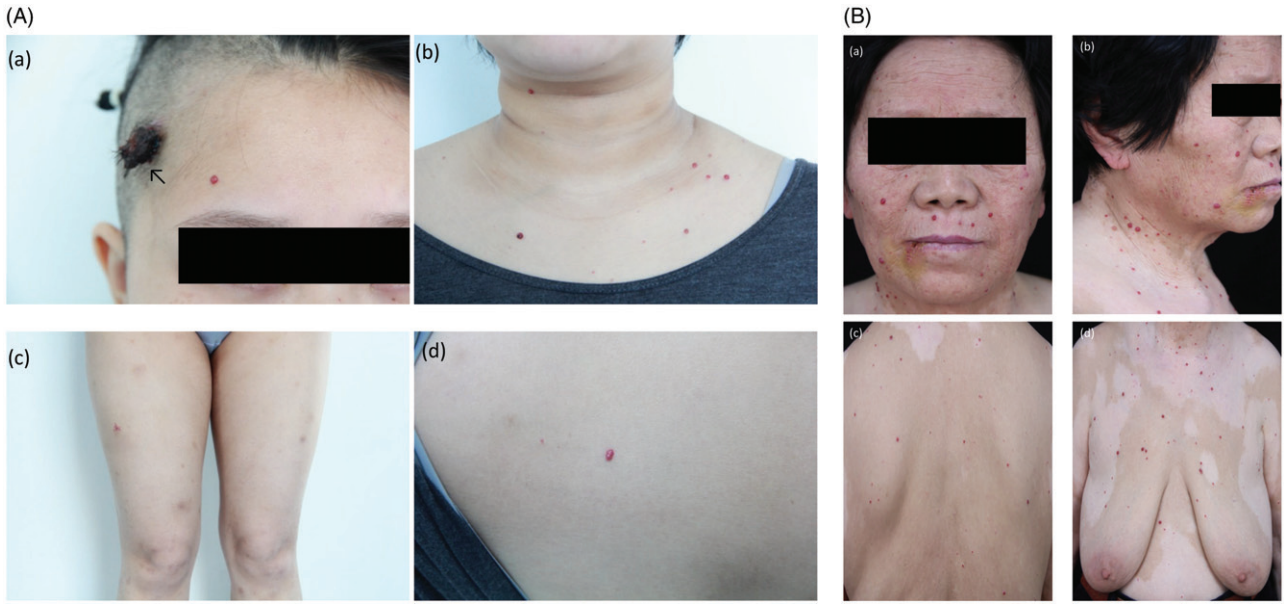

Figure 1. Clinical images. (A) lesions on the scalp (a), face (a), chest (b), thigh (c), and abdomen (d). (B) Multiple cherry angiomas on the face (a), neck (b), back (c), chest (d).

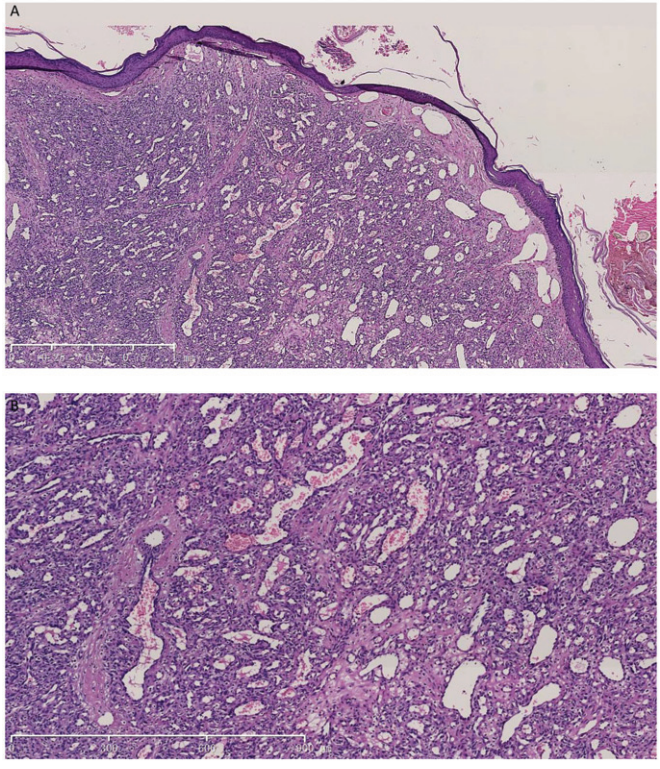

Figure 2. Histopathologic specimen of the nodule in case 1 shows numerous vascular spaces lined by endothelial cells, surrounded by fibromyxoid stroma and scattered inflammatory cells. (hematoxylin-eosin stain, original magnification × 12.5 (A), ×50 (B)).

et al., 83.3% of subjects developed reactive capillary hemangiomas, and this appeared to be dose dependent [8]. The mechanism of this phenomenon was still under investigation, with a possible explanation of a shift in the balance of receptor/receptor-ligand interactions with upregulation of vascular proliferative proteins (i.e. VEGF) [9]. It is an interesting observation that similar reactions have never been reported in other anti-PD-1 antibodies previously. Perhaps this is an idiosyncratic reaction specific to SHR-1210. These two cases present eruptive cherry hemangiomas induced by camrelizumab (SHR1210), an anti-PD-1 agent, adding to the spectrum of cutaneous reactions which may be observed in association with anti-PD-1 therapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Sheth S, Lai CK, Dry S, et al. Benign vascular tumors and tumor-like proliferations. Semin Diagn Pathol. 2008;25:1–16.
[2] Firooz A, Komeili A, Dowlati Y. Eruptive melanocytic nevi and cherry angiomas secondary to exposure to sulfur mustard gas. J Am Acad Dermatol. 1999;40:646–647.
[3] Borghi A, Benedetti S, Corazza M, et al. Detection of human herpesvirus 8 sequences in cutaneous cherry angiomas. Arch Dermatol Res. 2013;305:659–664.
[4] Lara PE, Medina-Puente C, Oliveira AR, et al. Eruptive cherry angiomas developing in a patient treated with ramucirumab. Acta Oncol. 2018;57:709–711.
[5] Fajgenbaum DC, Rosenbach M, Van RF, et al. Eruptive cherry hemangiomatosis associated with multicentric Castleman disease. JAMA Dermatol. 2013;149:204–208.
[6] Huang J, Xu B, Mo H, et al. Safety, activity and biomarkers of SHR-1210, an anti-PD-1 antibody, for patients with advanced esophageal carcinoma. Clin Cancer Res. 2018;24:1296–1304.
[7] Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. Lancet Oncol. 2018;19:1338–1350.
[8] Mo H, Jing H, Xu J, et al. Safety, anti-tumour activity, and pharmacokinetics of fixed-dose SHR-1210, an anti-PD-1 antibody in advanced solid tumours: a dose-escalation, phase 1 study. Br J Cancer. 2018;119:538–545.
[9] Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. Br J Dermatol. 2002;147:1270–1272.