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Letter to the Editor

Treatment of pembrolizumab-induced cutaneous lesions with ruxolitinib

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Dear Editor,

Immunotherapy is a fundamental part in the battle against cancer. The recent explosive progress and success of immune checkpoint inhibitors provide novel strategies for the treatment of a variety of cancers. Because of the novel and appealing mechanism in fighting cancer, many patients show increased interest in using checkpoint inhibitors for their inoperable malignancies. Thereafter, the associated immune-related adverse effects (irAEs) become a challenging issue for clinical practitioners. Patients with irAEs of grade 2 or a higher degree typically have their drug withheld and are treated using corticosteroids. Additional immunosuppressant may be used for patients in uncontrolled condition. However, some patients cannot tolerate or are unsuitable to corticosteroids or other immunosuppressants. Here, we report a case of successful treatment of pembrolizumab-induced cutaneous lesions with a Janus kinase inhibitor ruxolitinib, without other side effects.

1. Case report

A 66-year-old man received a diagnosis of adenocarcinoma of the ampulla of Vater with multiple liver metastases. His disease was controlled with paclitaxel and triweekly pembrolizumab administered at a dose of 100 mg intravenously. He developed grade II skin rash with dark erythematous patches with xerosis on the trunk and limbs after the first dose of pembrolizumab. During the treatment period, the symptoms improved and were under control by treatment with antihistamine in combination with low-dose prednisolone (0–5 mg per day) for the subsequent 6 doses of pembrolizumab. After the 8th dose of pembrolizumab, the skin lesions aggravated and became refractory to antihistamine and low-dose enteral prednisolone, with generalised erythematous scaly macules, papules and patches on the forearms, trunk and thighs and erosive wounds with yellowish discharge on the genital area. Prednisolone (50 mg per day parentally) was used to treat grade III skin lesions, but the patient complained of persistent hiccups on the second day. When prednisolone was tapered owing to hiccups, the skin rashes aggravated (Fig. 1A). To control the dermatological lesions without increasing the dose of prednisolone, ruxolitinib at a dose of 10 mg per day was administered orally. The skin lesions on the limbs and trunk

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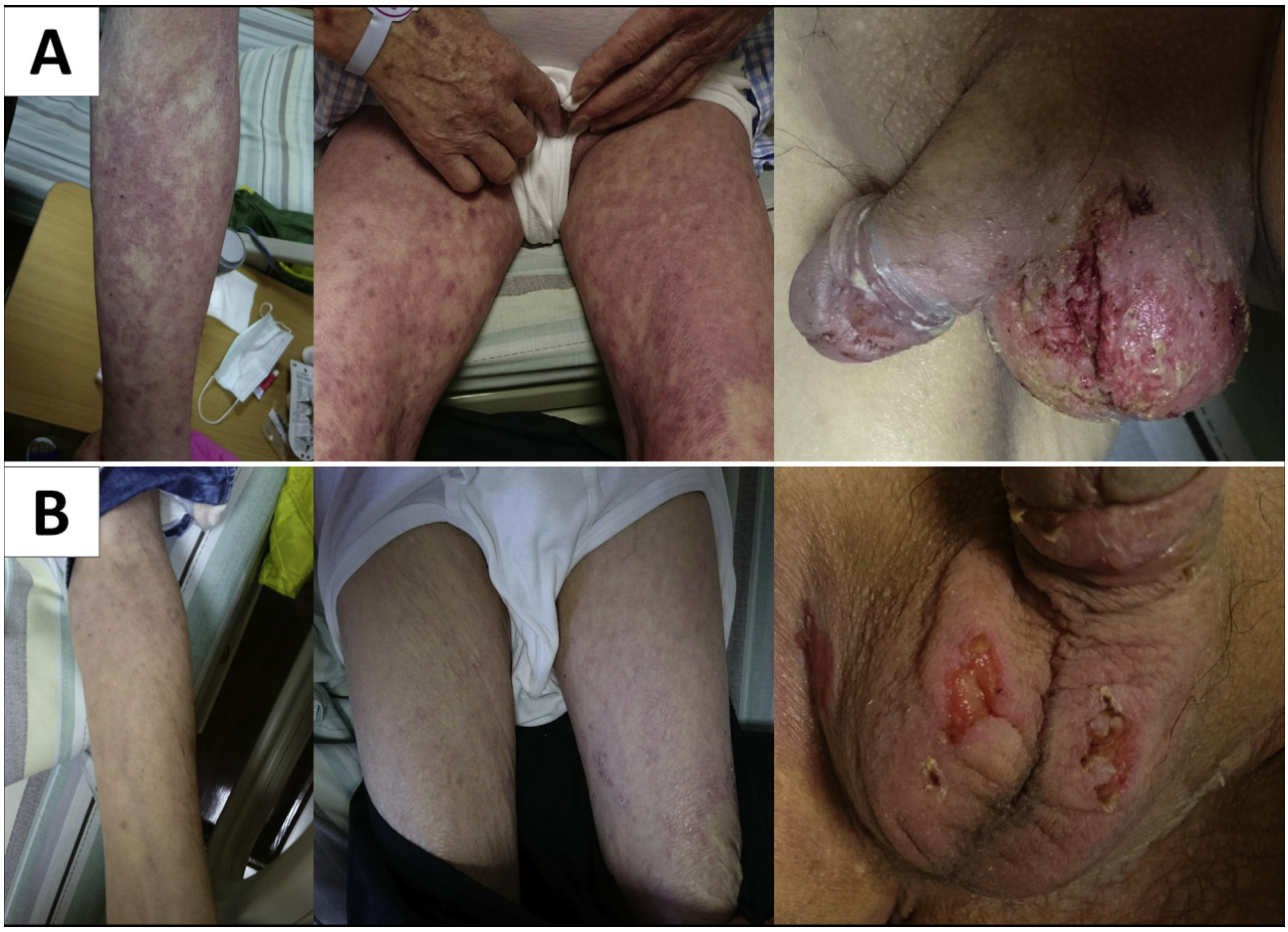

Fig. 1. Pembrolizumab-related skin rashes before and after ruxolitinib administration. (A) Before ruxolitinib administration, generalised erythematous scaly macules, papules and patches were observed on the forearms and thighs, and erosive wounds with yellowish discharge and hemorrhagic crust were observed on the scrotum, glans penis and shaft of the penis. (B) The skin lesions disappeared on the 7th day, and ulcerations of the scrotum improved greatly in the 3rd week after ruxolitinib administration.

improved substantially on the 3rd day and almost disappeared on the 7th day of ruxolitinib administration. The ulcerations of the scrotum improved at a lower rate, with healing observed after three weeks (Fig. 1B).

2. Discussion

Ruxolitinib, a selective Janus kinase 1/2 inhibitor, has been found to suppress the serum level of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, tumour necrosis factor (TNF)−α and interferon-γ [1], and to inactivate neutrophils and dendritic cells [2]. Ruxolitinib reduces tissue damage and alleviates fibrotic process through its anti-inflammatory actions. Clinically, ruxolitinib was first approved for use in patients with myelofibrosis after two randomised, double-blind, placebo-controlled phase III trials (COMFORT-I and II) [3,4]. Ruxolitinib effectively reduced the spleen volume, alleviated symptoms associated with myelofibrosis and improved the quality of life of patients. The major adverse effects of ruxolitinib were anaemia and thrombocytopenia, with grade III to IV adverse events observed in 22.5% and 15.2% of patients taking ruxolitinib, respectively [4]. In 2014, the US Food and Drug Administration (FDA) again approved ruxolitinib for polycythaemia vera based on the Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera trial. Besides its role in myeloproliferative disease, ruxolitinib was later found to be beneficial for patients with graft-versus-host disease (GVHD) after haematopoietic stem cell transplant. A retrospective, multicentre survey showed overall response rates of 81.5% and 85.4% and a median time to response of 1.5 and 3 weeks for corticosteroid-refractory acute GVHD and chronic GVHD, respectively [2]. Based on the preliminary results of a subsequent REACH1 (A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease) study, which showed an overall response rate of 55% on day 28 when treated with ruxolitinib in combination with corticosteroids, the FDA granted priority review for

ruxolitinib in October 2018 for the treatment of patients with acute GVHD who had an inadequate response to corticosteroids.

Pembrolizumab, exhibiting anticancer activity through targeting the programmed cell death 1 receptor of lymphocytes, has been widely used in various cancers, including melanoma, non–small cell lung cancer, head and neck cancer, urothelial carcinoma and gastrointestinal tract cancer with or without chemotherapy. Although it is undoubted that immune checkpoint inhibitors are active against certain cancer cells, it is well recognised that activated immune cells attack the normal body systems as well, resulting in irAEs. The potential mechanisms of irAEs include increasing T-cell activity against normal cells and the number of autoantibodies, inflammatory cytokines and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)–expressing normal tissues [5]. Corticosteroids are the first-line treatment for irAEs; however, for steroid-refractory irAEs, higher dose of steroids, mycophenolate mofetil, tacrolimus, anti–thymocyte globulin and anti–TNF-α have been used with variable success.

Our patient presented with pembrolizumab-induced generalised skin rashes over the limbs and trunk and painful scrotum ulcerations. The skin lesion exacerbated after the steroid was tapered for intolerable hiccups. Based on the recognition of ruxolitinib activity on GVHD and the similarity of pathophysiology between GVHD and irAEs, ruxolitinib was used to ameliorate the dermatological adverse effects for this patient. Notably, ruxolitinib showed efficacy without any adverse effect. To the best of our knowledge, this is the first report on the use of ruxolitinib in treating irAEs of immune checkpoint inhibitors. However, further clinical trials are needed to confirm this observation.

Conflict of interest statement

Dr. Chiu and Dr. Chen have nothing to disclose. Dr. Bai reports grants from the Ministry of Health and Welfare, Taiwan, (MOHW107-TDU-B-212-114026A) and the National Health Research Institutes, Taiwan (NHRI-108A1-CACO-13191902) during the study.

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