Acrixolimab-Induced Radiation Recall Dermatitis with Distinct Features Resembling Erythema Multiforme

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ABSTRACT:
Immune checkpoint inhibitors (ICIs), working against cancer cells by host immune system activation, have transformed the treatment and prognosis of many advanced cancers. ICIs commonly cause the well documented immune-related cutaneous adverse reactions. However, a rare cutaneous side effect, radiation recall dermatitis (RRD), an inflammatory skin reaction that occurs on the site of previous radiation and triggered by medications, has been recently reported. We present the first case of acrixolimab, a PD-1 inhibitor, induced RRD presenting with target skin lesions and central blisters in a 40-year-old Thai woman with stage IIIC malignant melanoma.
Key words: Radiation recall, radiation recall dermatitis, immunotherapy, immune checkpoint inhibitors, radiation therapy

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment paradigm of various advanced cancers by activating the immune system against cancer cells. Apart from well-documented immune-related adverse reactions such as maculopapular rash, psoriasiform rash, pruritus, eczema and lichenoid eruptions[1], ICIs also cause a rare cutaneous side effect, radiation recall dermatitis (RRD). To our knowledge, this is the first report of acrixolimab, a PD-1 inhibitor, induced RRD presenting with target skin lesions and central blisters resembling erythema multiforme.

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Report of case

A 40-year-old Thai lady received a diagnosis in July 2019 of stage IIIC malignant melanoma at the left knee (nodular type, Breslow thickness 5 mm with ulceration, regional lymph node metastasis) according to NCCN Clinical Practice Guidelines in Oncology. In April 2020, Radiation therapy (RT) following wide excision of the primary tumor, a total dose of 4,800 cGy, was delivered to the left knee towards the left groin area at a local hospital. In April 2021, she was referred to our oncology department since she developed disease recurrence with in-transit metastasis in the left thigh and bilateral inguinal lymphadenopathy. A CT scan revealed tumor progression, liver nodules and masses on the abdominal wall of which biopsy confirmed melanoma metastasis. Treatment with acrixolimab 200 mg every two weeks was administered from September 2021. Fifteen weeks after receiving acrixolimab, she developed individual target lesions coalescing into plaques, with blistering, erosions and crusting initially on the previously irradiated field, the left leg, and the left groin (Figure 1A and 1B) before spreading to involve the rest of the body (Figure 1C) with no mucosal involvement. Histopathology taken from the right thigh revealed vacuolar alteration of basal keratinocytes with subepidermal separation, individually scattered necrotic keratinocytes and superficial perivascular lymphocytic infiltrates (Figure 2A). Direct immunofluorescence study showed the deposition of IgM and C3 at cytoid bodies (Figure 2B and 2C). The erosions on the left leg were complicated with *Pseudomonas aeruginosa* infection identified by pus culture.

Regarding the distribution of the rash, beginning from the previously irradiated site and histopathological findings, acrixolimab-induced RRD was diagnosed. Three weeks after discontinuation of acrixolimab and introduction of a short course of prednisolone (0.5mg/kg/day) along with intravenous piperacillin/tazobactam, complete resolution of the skin lesions was observed. One month later, the diagnosis was confirmed by reappearance of the similar eruption predominately on the previously irradiated area and its consistent histopathological findings seven days after the culprit was re-administered. Due to the recurrence of skin lesions with grade 3 severity[2] upon drug re-administration, the immunotherapy was permanently discontinued in March 2022. Prednisolone was reintroduced (1 mg/kg/day) with good response.

Figure 1 Clinical images of cutaneous eruptions at initial visit
A. and B. Ulcers and erosions on the left leg and thigh with debris
C. Target lesions, blisters, and erosions on the chest wall
D. Target lesions, blisters, and erosions on the left arm

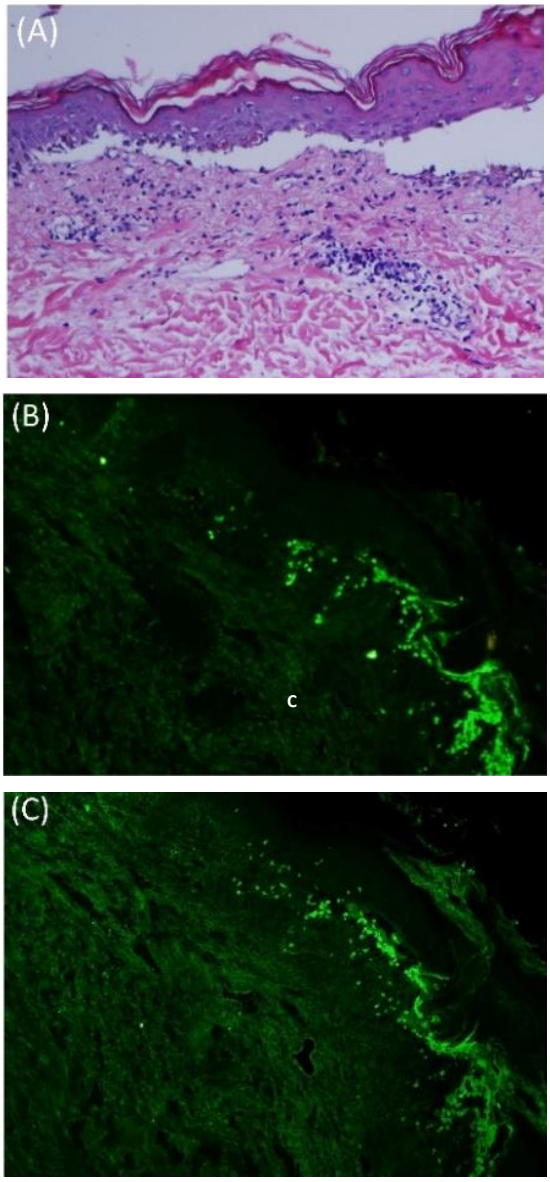

Figure 2 Histopathology and direct immunofluorescent study of a lesional biopsy specimen
A. Vacuolar alteration of basal keratinocytes with subepidermal separation, individually scattered necrotic keratinocytes and superficial perivascular lymphocytic infiltrates (H&E, X20)
B. Deposition of of IgM at cytoid bodies (DIF, X20)
C. Deposition of of C3 at cytoid bodies (DIF, X20)

Discussion

Radiation recall reaction (RRR) refers to inflammatory reaction at the previously irradiated site triggered by medication including conventional chemotherapy, molecularly targeted agents, and more recently ICIs[3]. The mechanisms of RRR are yet well understood. Several hypotheses had been proposed; stem cell inadequacy, idiosyncratic drug hypersensitivity, vascular damage and altered drug pharmacodynamics within irradiated field[4]. Cutaneous and pulmonary involvement have been most frequently reported[3], however, RRR may arise in sites of prior RT including oral mucosa, gastrointestinal system, genitourinary tract, muscle layer, central nervous system, head and neck. The presentations of RRD range from erythema, eczematous rash to severe forms, edema, blisters, and necrosis[3,4]. Our patient developed generalized severe bullous eruption followed by erosion and ulceration requiring culprit discontinuation and systemic glucocorticoid. Systemic immunosuppressive therapy should be particularly avoided in order to retain the anti-tumoral activity of ICIs. However, it is sometimes necessary when managing severe cases of cutaneous immune-related adverse reactions[5,6].

Twelve cases of ICI-induced RRD have been reported worldwide including our patient, among which the main culprit appears to be nivolumab[7-13]. Skin lesions associated with ICI-induced RRD vary from erythematous edematous rash[7-11,14,15] to severe manifestations, epidermal detachment with mucosal involvement, Stevens-Johnson syndrome (SJS) [12,13], which enhanced on the sites that were previously irradiated. Concomitant pneumonitis was reported in two cases[11,14]. The interval between RT and drug administration ranged from one week to 44 months. Interestingly, the duration between drug initiation and the onset of cutaneous eruption varied from hours to 110 weeks[7]. Histopathological analysis of ICI-

induced RRD cases showed subacute spongiotic dermatitis[7] while those presenting with SJS had pauci-immune interface dermatitis[12] with necrotic keratinocytes and areas of full-thickness epidermal necrosis with subepidermal separation.[12,13] In our patient, skin biopsy showed basal vacuolar alteration with individually necrotic keratinocytes, subepidermal separation and sparse superficial perivascular lymphocytic infiltrates. Deposition of IgM and C3 at cytoid bodies supported the diagnosis of bullous erythema multiforme.

In conclusion, we herein report the first clinical case of acrixolimab-induced RRD with the distinct cutaneous lesions of target lesion and central blister without mucosal involvement, confirmed by histopathological study, resembling bullous erythema multiforme initially in the previous radiation fields with subsequent dissemination. RRD is a rare condition encountered in clinical practice but should be kept in mind in the setting of previous RT and ICIs has become one of the most recent culprits.

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