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Case Report

Irradiation Field-Specific Suppression of Generalized Drug Eruption in a Cervical Cancer Patient : Reverse Koebner Phenomenon

Hiroshi SEKINE[1], Hitoshi MIZUTANI[2], Toshihiro ITO[3], and Ryusuke KAYA[4]

[1]*Department of Radiology, The Jikei University Daisan Hospital*
[2]*Department of Dermatology, Sakuragi Memorial Hospital*
[3]*Department of Dermatology, The Jikei University School of Medicine*
[4]*Department of Obstetrics and Gynecology, The Jikei University School of Medicine*

ABSTRACT

A drug eruption is a type of dermatitis due to hypersensitivity to medications. In contrast, radiation dermatitis is a nonspecific inflammation caused by physical injury of the skin cells by ionizing radiation. The severity of radiation dermatitis depends on the radiation dose. Anticancer agents are used with radiation therapy to enhance the anticancer effects but increase the risk of severe radiation dermatitis in the irradiated field. Here, we report a case of an interesting phenomenon—absence of drug eruptions in the radiation field during chemoradiotherapy—and discuss its mechanism. A 50-year-old woman received a diagnosis of stage IIB uterine cervical cancer and began concurrent chemoradiotherapy with cisplatin (40 mg/m^2) administered once a week. Four weeks after chemoradiotherapy began, generalized dermatitis developed, but the skin at the irradiated field of the pelvis remained unaffected. This rare phenomenon, called reverse Koebner phenomenon, was an unexpected effect of radiation on the skin. In the response of skin cells to radiation, many cytokines exhibit pleiotropy. Depending on the situation, various cytokines have both proinflammatory and anti-inflammatory potential. Reverse Koebner phenomenon might be due to the response of the innate immune system, triggered by irradiation, which locally suppresses the development of delayed-type drug hypersensitivity. (Jikeikai Med J 2023 ; 70 : 61-6)

Key words : drug eruption, chemotherapy, cervical cancer, radiotherapy, irradiation field, reverse Koebner phenomenon

INTRODUCTION

The severity of radiation dermatitis is dependent on radiation energy, fractionation dose, total dose, and treatment time, and its symptoms become more pronounced with lower radiation energy, higher fractionation dose, and higher total dose[1,2]. When radiation is applied as a treatment, its therapeutic effects are enhanced with various chemotherapeutic agents ; therefore, chemoradiation therapy is now routinely used for various malignancies and has increased local control rates[3-5]. However, the adverse effects of radiotherapy, including radiation dermatitis, are more severe in patients who also receive anticancer agents[6-8].

Radiation therapy causes inflammation in the skin of the targeted area but is unlikely to suppress dermatitis. A patient of ours who had recently undergone chemoradiotherapy for cervical cancer had a rare case of a generalized drug eruption that spared the radiation field. Herein, we re-

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關根　広，水谷　仁，伊藤　寿啓，嘉屋　隆介
Mailing address : Hiroshi SEKINE, Department of Radiology, The Jikei University, Daisan Hospital, 4-11-1, Izumi-Honcho, Komae, Tokyo 201-8601, Japan
Email : h-sekine@jikei.ac.jp

port this case and discuss the mechanism underlying the local suppression by irradiation of a generalized delayed-type hypersensitivity.

CASE REPORT

A 50-year-old woman had received a diagnosis of stage IIB uterine cervical cancer (tumor diameter, 45 mm ; poorly differentiated carcinoma). Immunohistopathologic analysis showed that the biopsy specimen was strongly positive for the marker protein p16, suggesting a human papillomavirus infection. Chemoradiotherapy was started (day 1) with 6 megavolts of photon beam (PRIMUS Mid-energy, Canon Medical, Ohtawara, Japan) accompanied by administration of cisplatin (40 mg/m^2) once a week (day 6). The course of treatment and laboratory data is shown in Table 1. After 17 fractions of radiotherapy had been given for a total radiation dose of 32.4 Gy (day 26), a fever (38.3°C) developed and a diffuse eruption developed symmetrically from the neck to the lower abdomen. The next day (day 27), the fourth dose of cisplatin was administered, but the eruption spread from the face to the lower extremities without mucosal reaction. Surprisingly, no eruption was found in the irradiation field of the pelvis, and the skin appeared unaffected (Fig. 1). Drug-induced lymphocyte stimulation tests (DLSTs) were performed for the medications, other than cytotoxic cisplatin, that were administered during the therapeutic period. The DLSTs for metoclopramide, prochlorperazine maleate, olanzapine, famotidine, and berberine chloride hydrate indicated within reference levels. Subclass-specific antibodies for rubella, measles, Epstein-Barr virus capsid and nuclear antigens, and cytomegalovirus were limited to the immunoglobulin G class, but not to the immunoglobulin M subclass, at low titers. On the basis of these findings, cisplatin-induced drug eruption was suspected[9].

Despite drug eruption being suspected, radiotherapy was continued. To treat the eruption, the patient was given the oral antihistamine olopatadine hydrochloride and the strongest topical corticosteroid clobetasol propionate. Although cisplatin was the agent suspected to have caused the eruption, at this time the only severe organ involvement was dermatitis. Thus, cancer treatment was prioritized, and the fifth dose of cisplatin was carefully administered (day 34) while anaphylactoid reactions were monitored with electrocardiography and the oxygen saturation via pulse oximetry[9]. After this administration, no specific adverse effect was observed. Eight days after topical therapy had been started, the generalized eruption gradually improved, and the skin lesions were completely attenuated within several days. External radiotherapy of 50.4 Gy and high-dose-rate intracavitary brachytherapy, administered 4 times, were completed on day 50 without adverse effects.

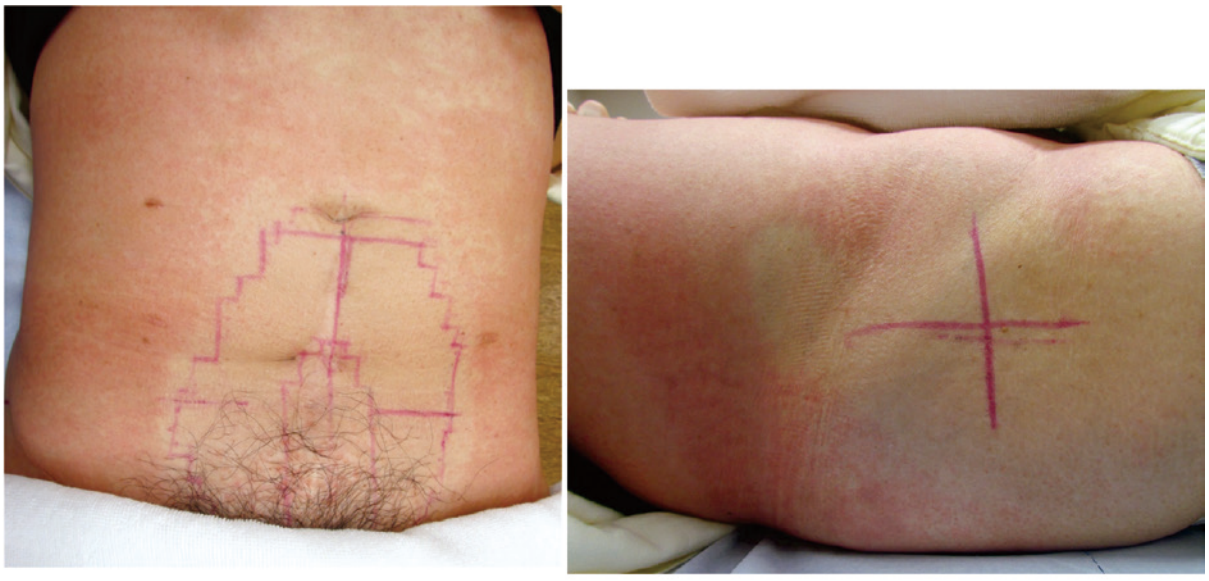
DISCUSSION

In the present patient, fever and generalized erythem-

Table 1. The course of treatment and laboratory data

Day		1	5	6	12	13	17	19	26	27	32	34	36	40	42	47	50
	Reference range																
White blood cells (10^3/μL)	3.3–8.6	–	3.7	–	3.7	–	4.6	–	2.5*	–	1.8*	–	–	–	–	–	–
Red blood cells (10^6/μL)	3.86–4.92	–	4.2	–	4.42	–	4.06	–	3.92	–	3.58*	–	–	–	–	–	–
Hemoglobin (g/dL)	11.6–14.8	–	12.5	–	13.3	–	12.3	–	11.7	–	10.9*	–	–	–	–	–	–
Platelets (10^3/μL)	158–348	–	187	–	187	–	156*	–	97*	–	104*	–	–	–	–	–	–
Neutrophils (%)	40.6–76.4	–	56.9	–	72.5	–	78.3†	–	85.4†	–	82.4†	–	–	–	–	–	–
Lymphocytes (%)	16.5–49.5	–	34.4	–	18.0	–	13.2*	–	6.7*	–	9.6*	–	–	–	–	–	–
Monocytes (%)	2.0–10.0	–	5.7	–	7.0	–	8.3	–	6.3	–	4.0	–	–	–	–	–	–
Eosinophils (%)	0.0–8.5	–	2.5	–	2.2	–	0.2	–	1.6	–	4.0	–	–	–	–	–	–
EBRT radiation dose (Gy)		1.8	5.4	7.2	14.4	16.2	21.6	23.4	32.4	34.2	39.6	43.2	45.0	46.8	50.4	–	–
ICBT													1	2		3	4
Cisplatin				1		2		3		4		5					

EBRT, external beam radiotherapy ; ICBT, number of intracavitary brachytherapy ; *, less than reference range ; †, greater than reference range



(A) (B)

Fig. 1. Eruption was suppressed over an area that corresponded to the field of pelvic irradiation. The indicated dose was 32.4 Gy in 18 fractions, and the mean skin dose estimated with fractionated radiotherapy was 17.6 Gy for the anteroposterior field (A) and 9.3 Gy for the lateral field (B).

atous dermatitis developed 7 days after the third dose of cisplatin was administered (day 26) and was exacerbated after the fourth dose (day 27). Results of the DLSTs were within reference levels for all administered medications except cisplatin. Antibody titrations for viral reactivation were negative. Unfortunately, cisplatin is a cytotoxic agent that is not suitable for the DLST. The skin eruption developed 3 weeks after the first dose of cisplatin. A literature review has found that hypersensitivity to cisplatin commonly develops from the fourth to eighth doses[9]. Thus, our patient was found to have a generalized drug eruption caused by cisplatin exposure.

The mechanism underlying a cisplatin-induced drug eruption is not completely clear. However, in several cases a delayed-type allergic mechanism has been suspected[9]. Cisplatin is a platinum-containing molecule that has been shown to have the potential to cause hypersensitivity reactions similar to metal allergy caused by Group 9/10 transition elements[10]. The skin is an organ in contact with factors outside the body. Langerhans cells (LCs), dendritic cells, and macrophages — called antigen-presenting cells (APCs) — reside in the epidermis and form a skin-associated lymphoid tissue to eliminate foreign antigens and denatured epidermal cells. When APCs recognize an administered medication (e.g., cisplatin) as a foreign antigen through Toll-like receptor 4 (TLR4) on the cells, TLR4 starts the transcription of cytokine genes, such as interleukin (IL)-6 and IL-8, through nuclear factor-kappa B or mitogen-activated protein kinase signaling[10]. TLR-mediated mechanisms are one of the initiation pathways of hypersensitivity reactions. In another mechanism, APCs that recognize an administered medication as a foreign antigen migrate to the regional lymph nodes and express the antigen on the major histocompatibility complex II to naive T cells, which then mature to form memory effector T cells. Effector T cells become helper T type 1 (Th1) cells in the presence of Th1 cytokines and induce CD8+ naive T cells to form antigen-specific cytotoxic T (Tc) cells. When epidermal cells are exposed again to the same medication after sensitization, they are recognized as the target cells by epidermal APCs and memory Tc cells. The cytokines, chemokines, and chemical mediators produced in the skin lesions recruit circulating Tc cells to target the skin, thus leading to exacerbated dermatitis.

Epidermal cell damage in radiation dermatitis results from the cytotoxic effects of radiation and from cytokines (IL-1, IL-3, IL-5, IL-6, tumor necrosis factor α, and transforming growth factor [TGF]-β), chemokines (eotaxin and

IL-8) produced by local epidermal cells, and adhesion molecules (intercellular adhesion molecule 1, E-selectin, and vascular cell adhesion protein) produced by the endothelial cells[11]. These cytokines, combined with the infiltrating inflammatory cells, exacerbate dermatitis. Radiation dermatitis is usually aggravated when radiation is combined with cytotoxic anticancer or molecularly-targeted agents, because of the synergistic cytotoxic effects.

In the present patient the generalized eruption began when the radiation dose was approximately 30 Gy. The mean skin dose, as calculated with the treatment planning system, was 17.6 Gy for the anteroposterior field and 9.3 Gy for the lateral field. Visually detectable radiation-induced erythema was not observed at this dose[12], even with possible aggravation by anticancer agents. A previous study has revealed that radiation exposure can induce drug hypersensitivity caused by cisplatin[13]. Concurrent chemoradiotherapy with cisplatin for cervical cancer caused drug hypersensitivity in 4 of 25 patients. Hypersensitivity reactions occurred after the first course in 2 patients, and after the third and fourth courses in 2 other patients. However, this study does not describe whether drug eruptions were suppressed within the irradiation field.

The generalized drug eruption in the present patient apparently spared the skin in the irradiated fields of the pelvis. As in this patient, the nonappearance of the characteristic lesions of a particular rash at the site of physical insult or previous disease is a rare condition. This condition has been given various names, such as "reverse Koebner phenomenon," "Koebner nonreaction," and "isomorphic nonresponse." Failure of drug rash to appear in a site that had undergone irradiation was the first documented sparing reaction[14]. Since then, nonexistence of a drug reaction in an area previously irradiated has been reported[15]. Psoriasis sparing of an area of a previously irradiated site has been reported for 1 patient[16]. The onset of skin lesions varied : during radiotherapy (accumulated dose, 5.85 Gy)[16], several days after the completion of radiotherapy (total dose, 25.0 Gy)[15], and 6 years after radiotherapy (total dose, 40.0 Gy)[14].

The absence of skin eruption might be due to local suppression of delayed type drug hypersensitivity in the irradiated skin by low doses of radiation. As a possible mechanism, TGF-β is produced from skin cells, including vascular endothelium, epidermal keratinocytes, and LCs, via exposure to sublethal doses of radiation[11]. After being produced, TGF-β suppresses leucocyte/vascular endothelial adhesion and acts on naive T-cells bound to APCs that become regulatory T (Treg) cells, which consequently produce TGF-β and IL-10[17-19]. The Treg cells suppress the activation of Th1 cells and the accumulation of Tc cells directly via TGF-β and IL-10 and suppress antigen-specific dermatitis[19]. In the field of dermatology, ultraviolet (UV) radiation therapies have been used to treat allergic and nonallergic skin diseases, including atopic dermatitis and psoriasis vulgaris[20]. Irradiation with UV induces keratinocytes to express the receptor activator of the nuclear factor-kappa B ligand (RANKL), which is a member of the tumor necrosis factor family. The RANKL then activates the epidermal LCs. Finally, the RANKL-stimulated LCs induce the proliferation of Treg cells in the UV irradiated skin[21-23]. Subsequently, obvious dermatitis cannot be induced in the irradiation field[24]. Although UV and photon beam have different physical properties, irradiated cells might respond somewhat similarly to electromagnetic waves. Cytokines exhibit pleiotropy, which means that the same cytokine might have different effects on different cell types. Depending on the situation, different cytokines might have the same activity, a term called redundancy. Numerous cytokines have both proinflammatory and anti-inflammatory potential[25,26]. Considering that cytokines often affect the synthesis of other cytokines, assisting or inhibiting a cytokine pathway might affect other cytokine pathways, leading to unpredictable implications[27].

The case presented herein provides insight into the biological effects on the skin's immune system of low-dose irradiation for cancer treatment.

CONCLUSION

In the present patient, generalized eruption developed during concurrent chemoradiotherapy. On the basis of laboratory data and a literature search, we conclude that the most probable cause of generalized eruption was a delayed-type drug hypersensitivity caused by cisplatin. Delayed-type drug hypersensitivity is a cell-mediated immunological (type IV allergy) response against medications acting as antigens or haptens. In this case, the radiation dose to the target was approximately 30 Gy, but the dose to the skin was less than 20 Gy. Radiation dermatitis rarely has observable symptoms at these doses and is unlikely to be observed

even with concurrent chemotherapy. The suppression of eruption within the irradiated field, despite the onset of generalized eruption, has been called "reverse Koebner phenomenon." The reason for this phenomenon can be considered as follows. With the start of irradiation, innate immunity is activated in the skin within the irradiation field, and cascade reactions are triggered by cytokines, chemokines, and chemical mediators secreted by keratinocytes, fibroblasts, vascular endothelial cells, and macrophages. These substances involved in immunity may suppress cell-mediated immunity within the irradiated skin. This case clearly shows that radiation can induce local immunomodulation.

Ethical statement

The Jikei University and The Jikei University Daisan Hospital do not require an application to the institutional review board for case reports. Informed consent was not required. However, as the Personal Information Protection Law prohibits the publication of personally identifiable information, this case is reported according to specific instructions.

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