Radiat Med (2007) 25:27–30
DOI 10.1007/s11604-006-0093-3

CASE REPORT

Erythema multiforme and Stevens-Johnson syndrome following radiotherapy

**Tadamasa Yoshitake · Katsumasa Nakamura
Yoshiyuki Shioyama · Tomonari Sasaki · Saiji Ooga
Madoka Abe · Yusuke Urashima · Kazunori Urabe
Hiromi Terashima · Hiroshi Honda**

Received: June 5, 2006 / Accepted: September 5, 2006

Abstract Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) are thought to be hypersensitivity syndromes with various causes, and radiotherapy might be one of the causes of these syndromes. We herein report two cases of EM/SJS following radiotherapy. The first case was a 63-year-old woman with breast cancer. At the end of postoperative radiotherapy with 60 Gy, severe pruritic erythema appeared in the irradiated area and spread over the whole body. She was diagnosed with EM by a skin biopsy. The second case was a 77-year-old woman with uterine cervical cancer who underwent postoperative radiotherapy. At a dose of 30.6 Gy, pruritic redness appeared in the irradiated area and the precordial region, and it became widespread rapidly with polymorphic transformation. Although without any histological confirmation, SJS was strongly suspected because of her pruritic conjunctivitis. Because both patients were given medicines during irradiation, radiotherapy may not be the only cause of EM/SJS. However, it should be noted that radiotherapy might trigger EM/SJS.

Key words Erythema multiforme · Stevens-Johnson syndrome · Radiotherapy

T. Yoshitake · K. Nakamura (✉) · Y. Shioyama · T. Sasaki · S. Ooga · M. Abe · Y. Urashima · H. Terashima · H. Honda
Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
Tel. +81-92-642-5695; Fax +81-92-642-5708
e-mail: nakam@radiol.med.kyushu-u.ac.jp

K. Urabe
Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Introduction

Erythema multiforme (EM) is generally a self-limiting eruption of the skin and mucous membranes. Rarely, the disease progresses to bullous formations over the skin and mucosal surfaces with accompanying constitutional symptoms known as the Stevens-Johnson syndrome (SJS).[1] EM/SJS are thought to be hypersensitivity syndromes due to various agents, most frequently drugs and infections. However, it is less well known that radiotherapy may be one of the causes of EM/SJS.[1–8] We experienced two cases of EM/SJS following radiotherapy and report them here.

Case reports

Case 1

A 63-year-old woman underwent conservative surgery for right breast cancer. She received 50 Gy in 25 fractions of radiotherapy through opposing tangential fields using photons with 10 Gy in five fractions of electron boost to the tumor bed. At first, only mild dermatitis appeared in the irradiated area at a dose of 52 Gy. However, the dermatitis evolved into pruritic erythema and appeared also in her left axilla at the end of radiotherapy (Fig. 1A). Six days afterward, the erythema spread over the whole body with a temperature of 38°C (Fig. 1B). Routine laboratory tests were normal, except for C-reactive protein (5.51 mg/dl).

She was referred to a dermatologist, and a skin biopsy was performed from an erythematous area of her left forearm. The section showed a mild perivascular infiltrate of acute and chronic inflammatory cells in the

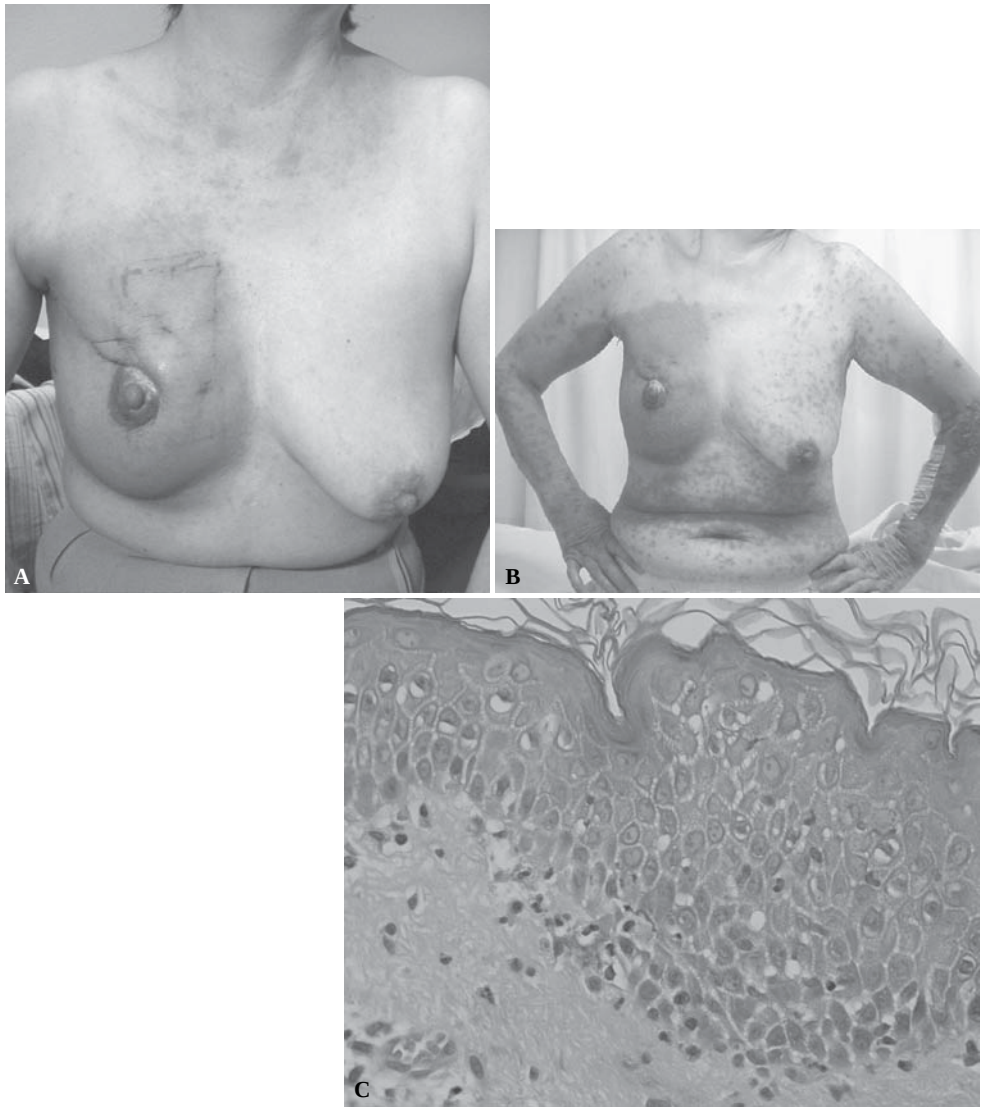

Fig. 1A–C. A 63-year-old woman underwent conservative surgery for right breast cancer. **A** At the end of the irradiation, a well-defined reddish change was seen in the irradiated area. Small reddish lesions were also scattered outside the irradiated area. **B** Six days after irradiation, the erythema had spread over the whole body. **C** Histological examination of the skin lesion of the left forearm showed a mild perivascular infiltrate of acute and chronic inflammatory cells in the upper dermis with vacuolar degeneration at the dermoepidermal junction

upper dermis with vacuolar degeneration at the dermoepidermal junction; these findings were compatible with EM (Fig. 1C). There was a possibility that anastrozole induced EM because she was administered anastrozole 1 mg per day as hormone therapy after the dose of 30 Gy. Anastrozole was discontinued immediately, and she was treated with systemic steroidal, antibiotic, and antihistaminic drugs. Thereafter, the erythema disappeared quickly. The patch test to anastrozole was performed after the alleviation of EM, but it was found to be negative. In addition, EM did not recur after she resumed administration of anastrozole.

Case 2

A 77-year-old woman with uterine cervical cancer stage Ib underwent total hysterectomy. Postoperative radiotherapy was planned to be delivered to the whole pelvis to a dose of 45 Gy because histological examination revealed the presence of lymphatic infiltration. At a dose of 30.6 Gy, pruritic redness appeared in the irradiated area and in the precordial region. It rapidly became worse and more widespread, with polymorphic transformation over the whole body with a temperature of 38.6°C. Despite administration of steroid ointment, antihistaminic ointment, and an oral antihistaminic drug, her condition deteriorated further (Fig. 2A). The white blood cell count (13 100/μl) and C-reactive protein level (6.7 mg/dl) were elevated, but other routine laboratory tests were within normal limits. She was diagnosed as having EM clinically by a dermatologist. Additionally, the progression to SJS was suspected because of her pruritic conjunctivitis.

Radiotherapy was terminated at a dose of 39.6 Gy, and a steroid and antibiotic were injected intravenously. Her fever resolved the next day. The erythema became

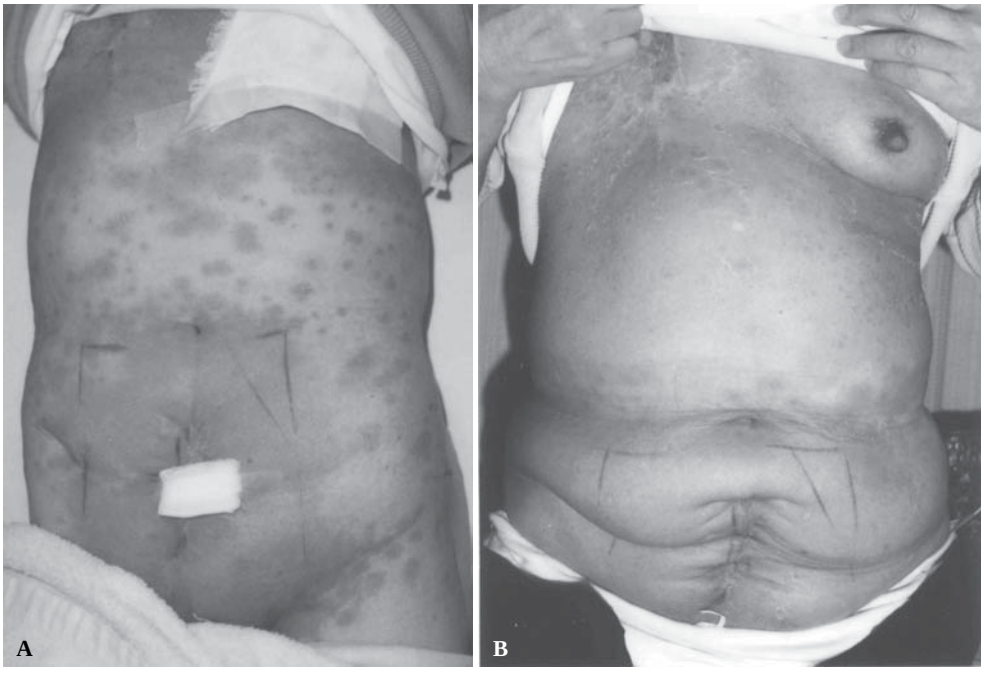

Fig. 2A,B. A 77-year-old woman with uterine cervical cancer. **A** At a dose of 39.6 Gy, the erythema extended widely, beyond the irradiated area. **B** Four days after administration of steroid and antibiotic, the erythema became crusted and desquamated

crusted and scaly and disappeared with pigmentation 7 days after the end of radiotherapy (Fig. 2B). Her medications at the onset of skin lesions were triazolam and rilmazafone, which were given before radiotherapy. There were no infections or other factors that were likely the causes of EM/SJS.

Discussion

Erythema multiforme, SJS, and toxic epidermal necrolysis (TEN) are reactive dermatoses involving a hypersensitivity state; they are defined as the same pathological condition according to current theory.[9] TEN is characterized by erosion of the mucous membranes, intensive disintegration in the epidermis, and severe constitutional symptoms. Causative factors such as some drugs, streptococcal infection, sarcoid, or tuberculosis may be identified in patients with these diseases, but no causative factors can be identified in many cases. Although the pathogenesis is still unknown, EM is believed to be an immunological disorder. Safai et al. found a high level of immune complexes and a low level of the complement component in the blister fluid, suggesting that immune complexes were activating complement components via classic pathways in the blister fluid of patients with EM.[10]

Irradiation causes various cutaneous adverse reactions. Acute radiation dermatitis in the irradiated area is the most common. However, EM/SJS related to radiotherapy, which is a rare manifestation of the adverse reactions, have been well documented since Holzknecht reported four cases of disseminated eruption with fever following irradiation of the head in 1903.[11] Most of patients in the literature were diagnosed as EM, SJS, or TEN clinically or pathologically,[1–8,12] and some were diagnosed as erythema nodosum or Sweet's syndrome.[13–15]

As for the mechanisms of EM/SJS as a result of irradiation, some hypotheses have been proposed. Delattre and coworkers reported eight patients with EM and SJS who were treated with both cranial irradiation and phenytoin for intracranial tumors.[7] They believed that phenytoin and irradiation acted together because two of their patients had no recurrence of eruption after resuming radiotherapy without phenytoin, and because they had not found a single case of EM after irradiation alone. In addition to the combination of phenytoin and cranial irradiation, there have been a few reports of the interaction of irradiation and other drugs causing generalized eruptions.[6,16] Although there were less popular hypotheses,[2,5,8,13,15] the mechanism of EM/SJS has not been elucidated. In addition, it is still unclear whether radiotherapy alone causes EM/SJS, as reported by several authors.[6,7]

Radical treatment of EM/SJS involves removal of the causative factors. Antihistamines and nonsteroidal antiinflammatory drugs can be used as symptomatic treatment for itching and pain. If cutaneous detachment affects a widespread area, treatment similar to that for a burn injury is needed. Eruption usually improves after 2–4 weeks, and the prognosis of EM is comparatively

good. However, if the symptoms progress to SJS or TEN despite treatment, the mortality risk increases significantly. Indeed, fatal cases of EM/SJS related to radiotherapy have been described in previous reports.[3,4] Moreover, in SJS, the eye condition as a sequela is critical. Dry eye, conjunctival adhesion, and corneal ulcer may remain and result in loss of sight after improvement of the body condition. Accurate diagnosis and early treatment are therefore important.

Conclusion

We reported two patients with EM/SJS following radiotherapy. Although we could not deny the possibility that the drugs or other factors might have caused EM/SJS in our patients, it should be noted that radiotherapy might trigger EM/SJS. During and after radiotherapy, clinicians should pay attention to the skin condition of the patients, keeping in mind the possibility of EM/SJS.

Acknowledgments. This study was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences.

References

1. Howell WR, Knight AL, Scruggs HJ. Stevens-Johnson syndrome after radiotherapy. South Med J 1990;83:681–3.
2. Ridgway HB, Miech DJ. Erythema multiforme (Stevens-Johnson syndrome) following deep radiation therapy. Cutis 1993;51:463–4.
3. Ahmed I, Reichenberg J, Lucas A, Shehan JM. Erythema multiforme associated with phenytoin and cranial radiation therapy: a report of three patients and review of the literature. Int J Dermatol 2004;43:67–73.
4. Khafaga YM, Jamshed A, Allam AA, Mourad WA, Ezzat A, Al Eisa A, et al. Stevens-Johnson syndrome in patients on phenytoin and cranial radiotherapy. Acta Oncol 1993;38:111–6.
5. Maiche A, Teerenhovi L. Stevens-Johnson syndrome in patients receiving radiation therapy. Lancet 1985;2:45.
6. Fleischer AB Jr, Rosenthal DI, Bernard SA, O'Keefe EJ. Skin reactions to radiotherapy—a spectrum resembling erythema multiforme: case report and review of the literature. Cutis 1992;49:35–9.
7. Delattre JY, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. Neurology 1988;38:194–8.
8. Nawalkha PL, Mathur NK, Malhotra YK, Saksena HC. Severe erythema multiforme (Stevens-Johnson syndrome) following telecobalt therapy. Br J Radiol 1972;45:768–9.
9. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92–6.
10. Safai B, Good RA, Day NK. Erythema multiforme: report of two cases and speculation on immune mechanisms involved in the pathogenesis. Clin Immunol Immunopathol 1977;7:379–85.
11. Holzknecht G. Fieberhafte Allgemeinerkrankung mit Exanthem bei Röntgendermatitis. Arch Dermatol Syph 1903;66:71–3.
12. Aguiar D, Pazo R, Duran I, Terrasa J, Arrivi A, Manzano H, et al. Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: a risk to consider. J Neurooncol 2004;66:345–50.
13. Takagawa S, Nakamura S, Yokozeki H, Nishioka K. Radiation-induced erythema nodosum. Br J Dermatol 1999;140:372–3.
14. Fearfield LA, Bunker CB. Radiotherapy and erythema nodosum. Br J Dermatol 2000;142:189.
15. Van der Meij EH, Epstein JB, Hay J, Ho V, Lerner K. Sweet's syndrome in a patient with oral cancer associated with radiotherapy. Eur J Cancer B Oral Oncol 1996;32B:133–6.
16. Lale Atahan I, Ozyar E, Sahin S, Yildiz F, Yalcin B, Karaduman A. Two cases of Stevens-Johnson syndrome: toxic epidermal necrolysis possibly induced by amifostine during radiotherapy. Br J Dermatol 2000;143:1072–3.