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LETTER TO THE EDITOR

# Erythema Multiforme after Radiotherapy with 5-fluorouracil Chemotherapy in a Rectal Cancer Patient

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Dear Editor:

Erythema multiforme (EM) is commonly induced by drugs, such as anticonvulsants, antibiotics, and allopurinol. Other potential triggers include herpes virus infection, *Mycoplasma* pneumonia, malignancy, connective tissue diseases, and radiotherapy. There have been rare reports of EM induced by 5-fluorouracil (5-FU) with or without radiotherapy[1-3]. We report a case of a rare skin reaction after chemotherapy with 5-FU and radiotherapy in a patient with rectal cancer. The condition was diagnosed as EM secondary to the interaction of radiotherapy and chemotherapy.

A 54-year-old man presented with pruritic, erythematous targetoid papules, and confluent macules on the buttocks, dorsum of the hands, and the ears for 5 days. Six months earlier, the patient had undergone surgery for stage T3N2M0 rectal cancer and had received postoperative concomitant radiotherapy and chemotherapy with 5-FU. The patient was administered chemotherapy with intravenous 5-FU 750 mg/day for 4 days in 1 month, and six cycles of chemotherapy at 1-month intervals were planned. After the third chemotherapy cycle, radiotherapy was added with 180 cGy/day for 28 days to give a cumulative dose of 5,040 cGy. However, skin lesions developed at the end of the twenty-sixth radiotherapy session, after 4,680 cGy, and 13 days after the fourth chemotherapy cycle. Physical examination revealed variously sized targetoid papules and confluent macules that initially developed on both buttocks, an irradiated site, and subsequently spread to the dorsum of the hands and the ears (Fig. 1). Laboratory test results, including white cell counts, antinuclear antibody, immunoglobulin E, and kidney and liver functions, were within normal limits. A herpes virus immunoglobulin G test was positive, but an IgM test was negative. Histopathology of a skin biopsy from the buttocks showed vacuolar alterations in the basal layer, and mild inflammatory perivascular infiltration, including many eosinophils in the dermis, which was consistent with EM (Fig. 2). The patient ceased radiotherapy and had symptomatic treatment. The lesions almost completely resolved after 2 weeks of treatment. The patient received a fifth cycle of chemotherapy with the same regimen, and 13 days later, EM recurred on the arms and legs (Fig. 3). The patient refused further chemotherapy because of the skin reaction, and the lesions resolved with antihistamine and steroid treatments. No rash developed over 1 year and 9 months of follow-up.

The combination of radiotherapy and chemotherapy is a well known cause of EM. In the case of EM induced by phenytoin and radiation, the acronym "EMPACT" (erythema multiforme associated with phenytoin and cranial radiation therapy) has been suggested[4]. Clinically, it is similar to our case in several aspects. It does not have an immediate skin reaction after drug exposure. The lesion arose initially from an irradiated area and spread to other sites after administration. Then, after re-administration of the drug, EM recurred. It is suspected that the eruption requires several days for the accumulation of active metabolites or immune complexes rather than the parent compound.

The interaction of 5-FU with radiation induced EM in our

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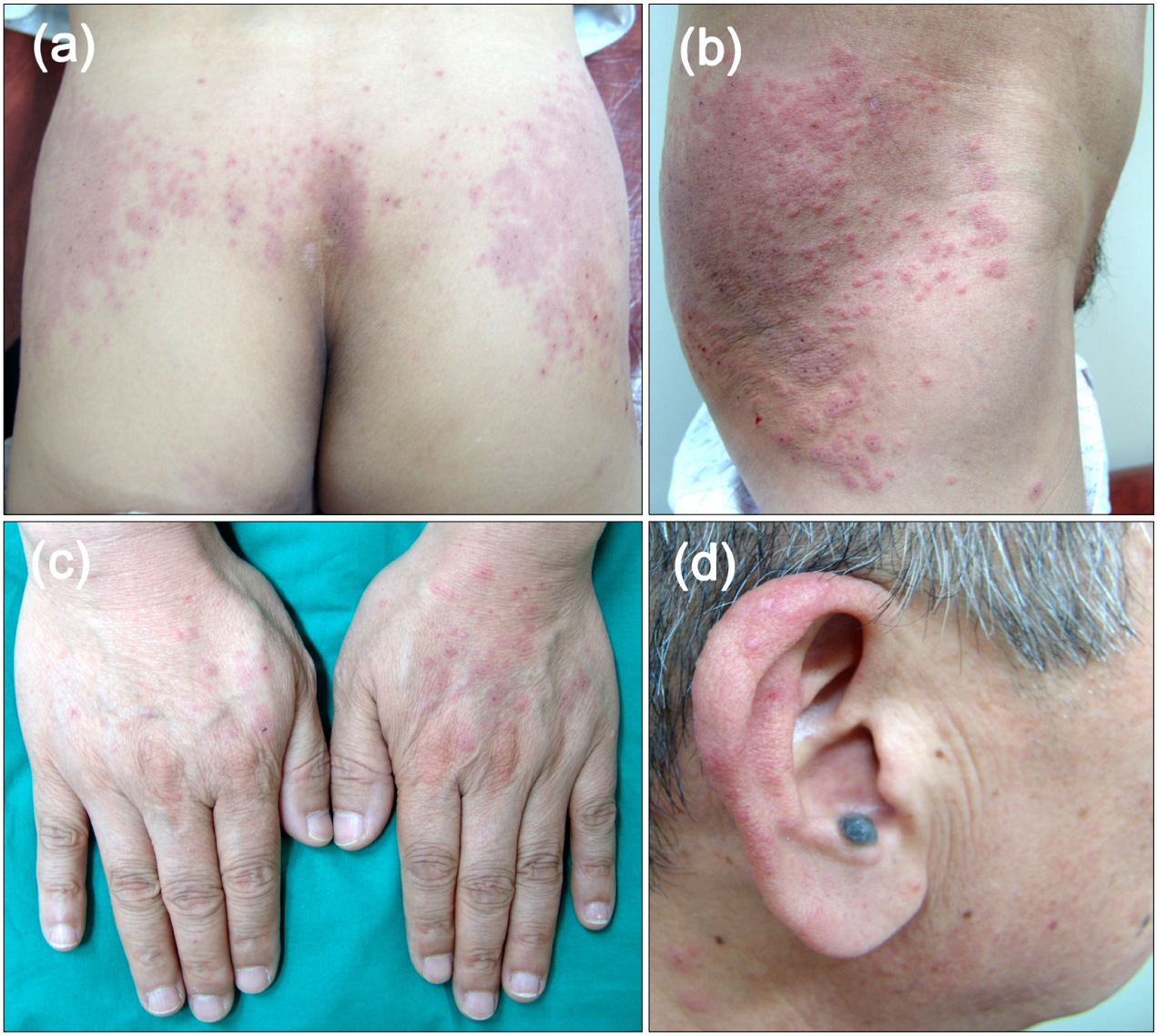


**Fig. 1.** At the first visit, erythematous targetoid papules and plaques were distributed on the buttocks (a, b), the dorsum of the hands (c), and the ears (d).

patient, and the pathological mechanism has several possible explanations. 5-FU is primarily eliminated by metabolism by dihydropyrimidine dehydrogenase. Although 5-FU is not a substrate for hepatic drug-metabolizing cytochrome P450 (CYP) enzymes, this antimetabolite may interfere with the synthesis of CYPs. Synthesis of CYP2C9 and CYP2C19, which are important in the metabolism of phenytoin, is decreased by 5-FU pre-treatment[5], which could explain why 5-FU-induced EM is associated with CYPs such as CYP2C9 and CYP2C19.

Furthermore, radiotherapy can enhance the primary antibody response, when administered shortly after immunization[6]. This can be explained by hypothesizing that suppressor cells are depleted, allowing for greater clonal expansion of sensitized cells that are free of feedback inhibition[7]. It is possible that radiotherapy preferentially impairs T-suppressor cells, thus allowing full development of a hypersensitivity reaction to the drug. Mediators induced by radiotherapy, such as kinins and histamine, could increase vascular permeability and facilitate entry of the new antigen into the circulation and induce an immune response[8]. These theories may also explain the greater likelihood of a drug reaction to 5-FU in the presence of radiotherapy, especially in the radiation field, and suggests that an increase in sensitivity and decrease in the threshold in radiated tissue lead to a hypersensitivity reaction upon exposure to 5-FU.

In conclusion, we report a case of EM secondary to the

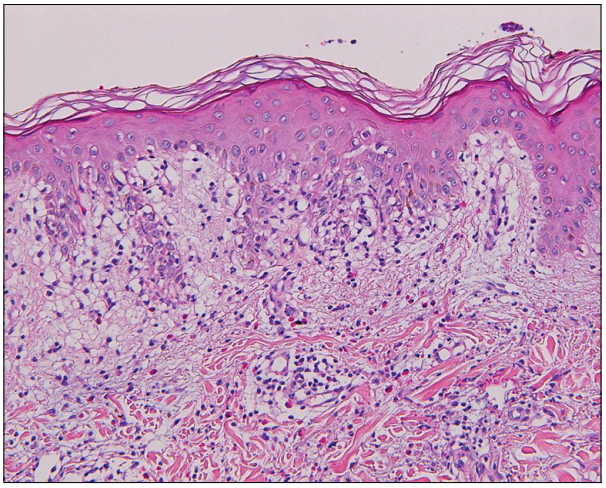

**Fig. 2.** Skin biopsy showing vacuolar changes in the basal layer, and mild perivascular inflammatory cells, including many eosinophils, infiltrating in the dermis (H&E, ×100).

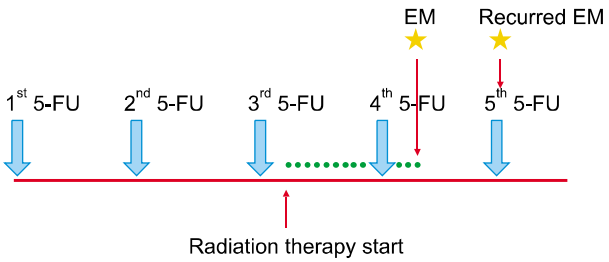


**Fig. 3.** Schematic representation of disease progression. After the third cycle of 5-FU administration, radiotherapy was added to the treatment, and EM developed after the fourth administration of 5-FU. Radiotherapy was stopped, and EM recurred following the fifth administration of 5-FU. 5-FU: 5-fluorouracil, EM: erythma multiforme.

interaction of radiotherapy and chemotherapy with 5-FU in a rectal cancer patient. Clinicians should be aware of the rare potential for 5-FU and radiotherapy to cause EM.

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