

## *A Case of Methotrexate-induced Bullous Acral Erythema*

Ye Won Han, M.D., Kyung Ho Lee, M.D., Chul Jong Park, M.D.

Department of Dermatology, College of Medicine, The Catholic University of Korea,  
Seoul, Korea

*Chemotherapy-induced acral erythema (CIAE) is a toxic reaction to a number of different chemotherapeutic agents, and causes symmetrical, well-demarcated, painful erythema on the palms and soles which is self-limiting. CIAE with bullous reaction in relation to methotrexate has been reported, but it is more commonly associated with cytosine arabinoside. The differential diagnosis of this condition from more serious conditions such as graft-vs-host disease or toxic epidermal necrolysis is essential.*

*In this paper, we report the case of a 65-year-old man who developed bullous acral erythema after the administration of high-dose methotrexate for the treatment of Non-Hodgkin's lymphoma. (Ann Dermatol (Seoul) 19(4) 160~162, 2007)*

---

Key Words: Methotrexate, Bullous acral erythema

### INTRODUCTION

Chemotherapy-induced acral erythema (CIAE) is an uncommon toxic reaction to a number of different chemotherapeutic agents. It is characterized by symmetrical, well-demarcated, painful erythema on the palms and soles which may progress to bullae formation and desquamation. The drugs most often involved in this eruption are fluorouracil, cytosine arabinoside and doxorubicin. CIAE with bullous reaction in relation to methotrexate has been reported, but is not a common phenomenon. CIAE resolves without any aggressive management, and therapy is generally supportive. Therefore, the differential diagnosis of this condition from more serious conditions such as graft versus host disease or toxic epidermal necrolysis is essential.

Herein, we report the case of a 65-year-old man who developed bullous acral erythema after the administration of high-dose methotrexate for the treatment of Non-Hodgkin's lymphoma.

### CASE REPORT

A 65-year-old man visited our hospital with a history of multiple palpable cervical lymph nodes for several months. The cervical lymph node biopsy was done and he was diagnosed as Non-Hodgkin's lymphoma, diffuse large B-cell type, in November 2000. He was treated with combination chemotherapy comprising 6 cycles of CHOP regimen (epirubicin, cyclophosphamide, vincristine and prednisolone) for six months, and had been in a tolerable state for 4 years without any cutaneous symptom or sign of tumor recurrence. However, the tumor recurred on the terminal ileum in October 2004. He was again treated with combination chemotherapy comprising 2 cycles of MACOB-B regimen (epirubicin and cyclophosphamide for the 1st cycle, vincristine and methotrexate for the 2nd cycle) for 2 weeks. 1 day after the completion of the 2nd MACOB-B chemotherapy including vincristine 1.4 mg/m<sup>2</sup> and methotrexate 360 mg/m<sup>2</sup>, painful erythema and bullous lesions developed on his soles (Fig. 1). There was no abnormal finding on physical examination except a dehydrated tongue. Initial laboratory investigations showed WBC 1,100/mm<sup>3</sup> (seg: 28%), BUN/Cr 44.3/1.65 mg/dL. The 24 hour urine chemistry was examined for the calculation of creatinine clearance rate, 58.1 mL/min. The methotrexate level of the serum was 0.04

---

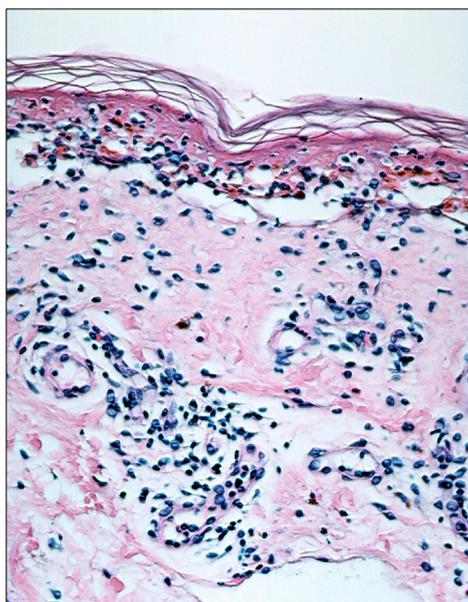
Received December 16, 2007

Accepted for publication July 24, 2007

**Reprint request to:** Chul Jong Park, M.D., Department of Dermatology, College of Medicine, The Catholic University of Korea, Tel: 82-32-340-2115, Fax: 82-32-340-2118, E-mail: holyderma@catholic.ac.kr



**Fig. 1.** Symmetrical, well-demarcated, painful erythema and bullous lesions on both soles.



**Fig. 2.** Epidermal necrosis, exocytosis, spongiosis, vacuolar degeneration of basal cell layer and subepidermal bulla with perivascular mononuclear cell infiltration in upper dermis (H&E,  $\times 200$ ).

$\mu\text{mol/L}$ .

A skin biopsy was completed on the lesion of the sole. The biopsy specimen showed epidermal necrosis, exocytosis, spongiosis, vacuolar degeneration of

basal cell layer and subepidermal bulla with perivascular mononuclear cell infiltration in upper dermis (Fig. 2).

The patient was placed on the topical therapy with high-potent corticosteroid ointments, his symptoms improved rapidly. Marked desquamation was observed in these lesions over the next 5 days, and the cutaneous lesions resolved completely. He completed 5 additional courses of MACOB-B without recurrence of the lesions.

## DISCUSSION

Chemotherapy-induced acral erythema (CIAE) is a localized cutaneous reaction to chemotherapeutic agents administered in patients with either hematologic malignancies or solid tumors. It is characterized by symmetrical, well-demarcated, painful erythema on the palms and soles which may progress to bullae formation and desquamation. Occasionally extension to periungual areas and over the dorsa of the hands and feet is observed<sup>1</sup>. It usually occurs between 1 day and 3 weeks after the start of chemotherapy, and most cases are resolved within 1 to 2 weeks with desquamation of the skin followed by reepithelization<sup>2</sup>. The histopathologic findings seen in CIAE include spongiosis, necrotic keratinocytes, nuclear pleomorphism, vacuolar changes and subepidermal bullae<sup>3</sup>. It appears to be a dose-dependent, toxic reaction caused by chemotherapeutic agents, but the pathogenesis remains unknown. Subsequent direct toxicity of the agent to the eccrine gland excretion has been proposed as a mechanism for the acral erythema<sup>4</sup>. Morrell et al<sup>4</sup> reported that the occurrence of CIAE was dependent on the dose rate, implying not only the accumulated dose of drugs administered but the amount of drugs administered over time. Diminished elimination of chemotherapeutic agents may be a potential risk factor for the development of bullous variant acral erythema<sup>5</sup>. Although excretion of the methotrexate in our case was not delayed, he had completed his 2nd cycle of chemotherapy at the out-patient clinic with insufficient hydration. Moreover, he was hospitalized for insufficient hydration, and completed 5 additional courses of MACOB-B without recurrence of the lesions. Therefore, the dehydrated state may be another potential risk factor.

Multiple chemotherapy agents have been implicated, including 5-fluorouracil, cytosine arabinoside, doxorubicin, methotrexate, paclitaxel, mercaptopurine, cyclophosphamide, mitotane, hydroxyurea, etoposide, docetaxel and taxol<sup>3</sup>. CIAE with bullous reaction in relation to methotrexate has been reported, but is more commonly associated with cytosine arabinoside<sup>5</sup>. In our case, combination and subsequent administration of multiple chemotherapeutic agents including epirubicin, cyclophosphamide, vincristine and methotrexate may have been a more likely contribution to the development of the reaction. However, he had been in a tolerable state without any cutaneous symptom for the combination chemotherapy comprising 6 cycles of CHOP regimen including vincristin. So we do not think that vincristine would have contributed to the development of CIAE in 2nd MACOP-B regimen composed of vincristin and methotrexate. These findings suggest that methotrexate, which was newly administered, is the most probable candidate for the causative drug in our case.

Therapy is generally supportive and consists of emollients and cold compressives<sup>3</sup>. In some cases, bullous acral lesions can preclude further use of the causative agent due to severe pain and impairment of function. When future cycles of the agent are necessary, patient-controlled analgesia, systemic methylprednisone, pyridoxine, and supportive topical treatments have been used to treat acral erythema. In patients with known bullous acral erythema, short courses of intravenous dexamethasone given at each infusion of the causative agent seem to limit bullae formation, narcotic use, and functional impairment<sup>4</sup>. But the data is anecdotal and no controlled studies have been performed. Our patient obtained substantial benefit from supportive topical steroids in the management of his acute symptoms.

It is often difficult to distinguish between CIAE and acute graft versus host disease (GVHD) in the early stages and they sometimes occur together, making correct diagnosis particularly challenging<sup>3</sup>. However, acute GVHD can arise almost exclusively in allograft recipients, and is often associated with

gastrointestinal disturbance and liver dysfunction. Although both conditions demonstrate acral erythema, the rash of acute GVHD typically appears on the face and upper chest first, and spreads to acral areas later. It may also become generalized and develop a papular component. Most importantly, whereas CIAE resolves without aggressive management and does not pose a threat to the patient's health, acute GVHD requires prompt intervention and may be fatal<sup>6</sup>.

High-dose methotrexate-induced acral erythema is not a common event. In the patient with spontaneous self-limiting evolution of the cutaneous lesions and without other signs of methotrexate toxicity, the chemotherapeutic schedule should not be modified in almost cases<sup>1</sup>.

Herein, we report a case of a 65-year-old man who developed bullous acral erythema after the administration of high-dose methotrexate for the treatment of Non-Hodgkin's lymphoma.

## REFERENCES

1. Millot F, Auriol F, Brecheteau P, Guilhot F. Acral erythema in children receiving high-dose methotrexate. *Pediatr Dermatol* 1999;16:398-400.
2. Azurdia RM, Clark RE, Friedmann PS. Chemotherapy-induced acral erythema (CIAE) with bullous reaction. *Clin Exp Dermatol* 1999;24:64-66.
3. Werchniak AE, Chaffee S, Dinulos JG. Methotrexate-induced bullous acral erythema in a child. *J Am Acad Dermatol* 2005;52:S93-95.
4. Morrell DS, Challengren E, Eapen M, Esterly NB. Bullous acral erythema secondary to high-dose methotrexate. *J Pediatr Hematol Oncol* 2002;24:240.
5. Hellier I, Bessis D, Sotto A, Margueritte G, Guilhaou JJ. High-dose methotrexate-induced bullous variant of acral erythema. *Arch Dermatol* 1996;132:590-591.
6. Crider MK, Jansen J, Norins AL, McHale MS. Chemotherapy-induced acral erythema in patients receiving bone marrow transplantation. *Arch Dermatol* 1986;122:1023-1027.