Management of Cyclosporine-worsening acral erythema

Chayanee Likitwattananurak MD,
Waroonphan Leecharoen MD,
Waranya Boonchai MD.

ABSTRACT:

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DEPARTMENT OF DERMATOLOGY, FACULTY OF MEDICINE, SIRIRAJ HOSPITAL, MAHIDOL UNIVERSITY, BANGKOK, THAILAND.

Acral erythema is one of the acral variants of toxic erythema caused by chemotherapy. Our patient demonstrated acral erythema secondary to cytosine arabinoside. During stem cell transplantation, cyclosporine administration was given, but it worsened the acral erythema. We suggest that a new, easy, and effective treatment to relieve the symptoms is simply a decreased cyclosporine infusion rate. We report the infrequent cutaneous adverse effects of worsening acral erythema caused by cyclosporine infusion and its management.

Key words: Acral erythema, cyclosporine

From: Department of Dermatology, Faculty of Medicine, Siriraj Hospital Mahidol University, Bangkok, Thailand
Corresponding author: Waranya Boonchai MD, email: waranya.boonchai@gmail.com

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Introduction

Acral erythema, also termed palmoplantar erythrodysesthesia, hand-foot syndrome, or Burgdorf's reaction, is one of the acral variants of toxic erythema caused by chemotherapy. Intensely painful erythema, desquamation, and edema of the palmoplantar areas accompany high-dose chemotherapy. Blister formation, developing into desquamation, has been reported in some cases[1–3]. Painful erythematous patch(es) usually appear 24 hours to 3 weeks following the initiation of certain chemotherapies. The pathogenesis is not well-defined. It is believed that the eccrine glands that are accumulated around the palms and soles are targeted by toxic chemotherapy. Palmoplantar erythema is caused by common chemotherapeutic drugs, including 5-fluorouracil, methotrexate, cytosine arabinoside, doxorubicin, and cytarabine. The adverse effects of acral erythema can cause patient discomfort, leading to the chemotherapy being discontinued[1–4].

Case presentation

We report the case of a 41-year-old Thai female diagnosed with B-cell acute lymphoblastic leukemia (ALL). The induction and consolidation phases of chemotherapy were prescribed for the patient following relapse of her disease. The FLAG-IDA regimen (fludarabine, cytosine arabinoside, and idarubicin) was given intravenously. The patient had a history of acral erythema with desquamation during the FLAG-IDA regimen administration, most likely caused by the cytosine arabinoside.

Two months later, the ALL was treated with a sibling-donor allogeneic stem cell transplantation, following which the patient received busulfan and melphalan as a conditioning regimen. Her palmar area still remained desquamative and mildly erythematous as a result of the previous combination chemotherapy. Intravenous cyclosporine (3 mg/kg/day) and intravenous methotrexate were also given as an acute graft-versus-host disease (aGvHD) prophylaxis. In accordance with the aGvHD prophylaxis protocol, cyclosporine was administered to the patient throughout the stem cell engraftment, and methotrexate was given on Day 11 after the stem cell initiation. The cyclosporine was infused over a 2-hour period twice daily (every 12 hours). However, she complained of an intense and worsening pain at both palmar areas that was significantly secondary to the cyclosporine infusions. The instillations were clearly provoking the intense palmar erythema as the symptoms were relieved whenever the infusions were ceased or the infusion rate was reduced from 2- to 3-hourly intervals. Recurrence of the pain and erythema occurred if the infusion dosage was restarted. Repetitive administration of the

cyclosporine aggravated the intensity of the pain at both palmar areas (Figure 1a). The patient denied other systemic symptoms, such as fever, nausea, diarrhea, or abdominal pain. Engraftment of the stem cell transplantation was achieved on Day 24 after transplantation. Unfortunately, skin biopsy was not done to confirm histological finding in this patient.

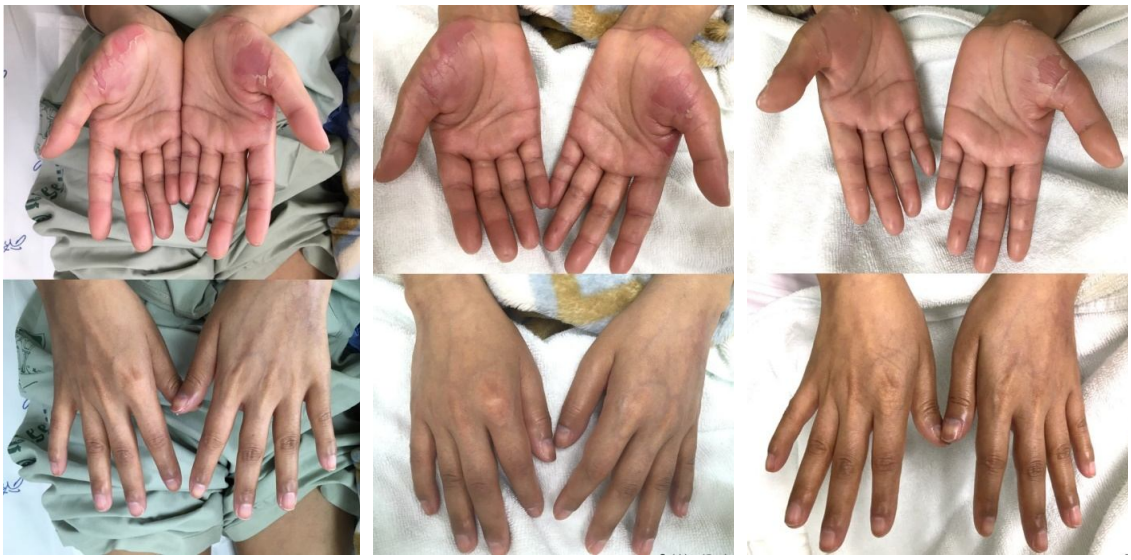

Figure 1A **Figure 1B** **Figure 1C**

Figure 1 A) Well-circumscribed edematous erythema on both the palmar and dorsal surfaces of the hands.
B) Remaining edematous erythematous of acral erythema after 2 hours of a cold-water soak.
C) Less edematous erythematous of acral erythema after decreasing the cyclosporine infusion rate.

Discussion

To date, there have been no previous reports of acral erythema being directly caused by cyclosporine. However, chemotherapy-induced painful erythema of the palmar area that was aggravated by intravenous cyclosporine, as in our case, has been reported previously, but only by two studies. As with the current patient, the earlier cases involved allogeneic stem cell transplantation, and cyclosporine administration had been given as an aGvHD prophylaxis[5,6]. In the first report in 1989, two patients who had been diagnosed with ALL experienced cytosine arabinoside-induced acral erythema. They complained that the cyclosporine infusion worsened their acral erythema. Their symptoms subsequently improved with meperidine and intravenous morphine[5]. As to the second report

in 2013, a 30-year-old ALL patient undergoing allogeneic stem cell transplantation demonstrated palmar redness secondary to cytosine arabinoside. He also complained of worsening pain around his palmar area upon each cyclosporine infusion; that pain was alleviated by a combination of analgesics, cold-water immersion, and decreased drug dosage[6].

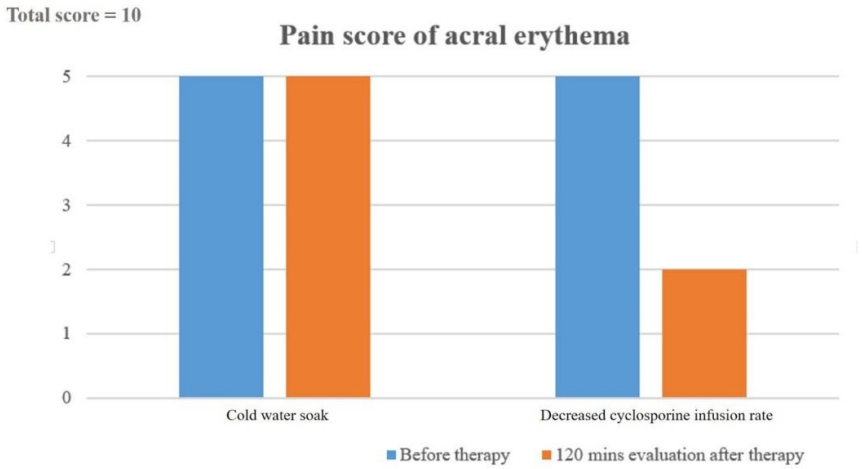

Figure 2 Comparison of the pain scores of the cold-water soak and the decreased cyclosporine infusion rate.

Acute GvHD is considered as a differential diagnosis in every reported burning palmar erythema case. However, in the present case, the cyclosporine was considered as a definite cause because the symptoms of the acral erythema became aggravated upon each infusion. One of the hypotheses mentioned in previous studies was that the alcohol content of cyclosporine infusions acts as an irritant ingredient. In addition, the alcohol in both the oral and intravenous cyclosporine formulas may exacerbate earlier palmar redness resulting from injury by cytosine arabinoside. We estimated that the alcohol concentrations of the cyclosporine formulations studied in previous case reports ranged from 32.9% to 33.18%. In the case of our patient, a 34.4% alcohol concentration was administrated, which is consistent with the earlier reports.

With our patient, it was found that applying topical 10% urea combined with 0.1% triamcinolone cream to lesions twice daily was of no benefit. From the beginning, our patient reported a pain score of 5 out of 10 for the intense acral erythema. Although 45 minutes of a cold-water soak was applied to relieve the palmar discomfort, the score was still persisting at 5 after

2 hours. The cold-water immersion therefore did not appear to be an efficient treatment modality (Figure 1B). By contrast, slowing the cyclosporine infusion rate from two hourly to three hourly reduced the pain score to 2 out of 10 (Figure 2), and the edema and erythema at both palms improved (Figure 1C). Nevertheless, these symptoms were moderately subjective and difficult to evaluate.

Conclusion

We have reported the rare cutaneous adverse effect of worsening acral erythema caused by a cyclosporine infusion. Simply decreasing the dosage of the cyclosporine infusion proved to be the most effective means of relieving the pain symptoms. All physicians should be aware of this rare incidence of cyclosporine administration. Its presence may unnecessarily disturb the quality of life of leukemia patients in addition to the suffering that they will inevitably experience from the side effects of chemotherapy.

Potential Conflicts of Interest All authors have neither conflicts of interest nor financial support to declare.

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