Intravenous Immunoglobulin in the Treatment of Severe Methotrexate-induced Acral Erythema

Hasan Tezer, MD, Barıs Kuskonmaz, MD,† Ates Kara, MD,* Ilker Devrim, MD,* Murat Tuncer, MD,† Ali Bulent Cengiz, MD,* Sevgi Yetgin, MD,† and Gülten Seçmeer, MD**

Summary: Chemotherapy-induced acral erythema is an uncommon and dramatic reaction to high-dose chemotherapy. It is characterized by painful erythema of both palms and soles with symmetrically well-defined borders, which may progress to bullae formation and desquamation. The bullous variant of this reaction has been reported with methotrexate and more frequently cytosine arabinoside. Rapid differential diagnosis and discrimination from more serious conditions such as graft versus host disease or toxic epidermal necrolysis is essential. In this case report, we present a 13-year-old boy who developed severe and prolonged chemotherapy-induced acral erythema after high-dose methotrexate treatment and successfully responded to intravenous immunoglobulin.

Key Words: chemotherapy side effect, acral erythema, methotrexate, intravenous immunoglobulin

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Acral erythema is characterized by painful erythema of both palms and soles with symmetrically well-defined borders, which may progress to bullae formation and desquamation. It is a localized chemotherapy-induced cutaneous response that has been observed in patients with either hematologic malignancies or solid tumors. Chemotherapy-induced acral erythema (CIAE), first described in 1982, is a localized cutaneous response to various chemotherapeutic agents including 5-fluorouracil,[1] paclitaxel,[2] mercaptopurine, doxorubucine, and cytosine arabinoside.[3,4] The bullous variant of this reaction has been reported in relation to methotrexate and more frequently cytosine arabinoside treatment.[5,6] The reaction usually begins with palmoplantar dysesthesia, causing symmetrical erythema with well-demarcated borders and blistering and eventual desquamation that remains limited to the palms and soles.[7]

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From the *Pediatric Infectious Disease Unit; and †Pediatric Hematology Unit, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara Turkey.

Reprints: Ates Kara, MD, Department of Pediatrics, Pediatric Infectious Disease Unit, Hacettepe University Faculty of Medicine, Hacettepe 06100 Ankara Turkey (e-mail: ateskara@hacettepe.edu.tr).

We describe a case of CIAE with bullous reaction in a 13-year-old boy with acute lymphoblastic leukemia treated with methotrexate. Our case is different from the cases in literature with extensive involvement of lesions that progressed despite supportive treatment and responded successfully to intravenous immunoglobulin (IVIG) therapy.

CASE REPORT

A 13-year-old boy admitted to the hospital with weakness, nausea, vomiting, and bloody diarrhea. His history was remarkable for acute lymphoblastic leukemia, diagnosed 1 year ago. He was in remission and under maintenance chemotherapy. The patient had a history of high-dose methotrexate treatment ($2\,g/m^2$) 3 days before the development of his complaints. His white blood cell count, hemoglobin level, and platelet count were $4500/mm^3$, 10.7 g/dL, and $139{,}000/mm^3$, respectively. Absolute neutrophil count was $2550/mm^3$. His vital signs were as follows: axillary body temperature, 38.4°C; heart rate, 120/min; respiratory rate, 20/min; systolic and diastolic blood pressure, 100/70 mm Hg. Physical examination revealed no pathologic findings. He was hospitalized and treated with intravenous ceftriaxone for the diagnosis of gastroenteritis. On the second day of his hospitalization, ceftriaxone therapy shifted to teicoplanin and ciprofloxacin because he had developed neutropenic fever episode with fever (38.6°C). On the second day of hospitalization, he developed painful erythema localized to both of the palms and soles (Figs. 1A, B). One day later, he had developed edematous, painful, red, violaceous erythema developed on the hands, feet, and toes bilaterally. The erythema on his feet progressed to bullous formation (Fig. 2). He had similar lesions on several other areas of his body (Fig. 3), the lesions on the mouth, lips, and perianal areas desquamated and progressed to painful ulcers. He was treated with topical moisturizers and supportive therapy. Despite supportive treatment, he had developed severe dysphagia and retrosternal pain; total parenteral nutrition (TPN) had been initiated because he had difficulty in swallowing or eating. At the end of the fifth day of his hospitalization, amphotericin B was added to the therapy because of his resistant fever. His bloody diarrhea progressed up to 10 defecations per day. Because of his deteriorating clinical condition IVIG therapy was added to his therapy (0.4 g/kg/d, for 5 consecutive days) at the seventh day of hospitalization. His bloody diarrhea was recovered and his oral intake improved after treatment with IVIG. All the lesions, including lesions on mucosa and perianal region, recovered within 3 weeks after therapy.

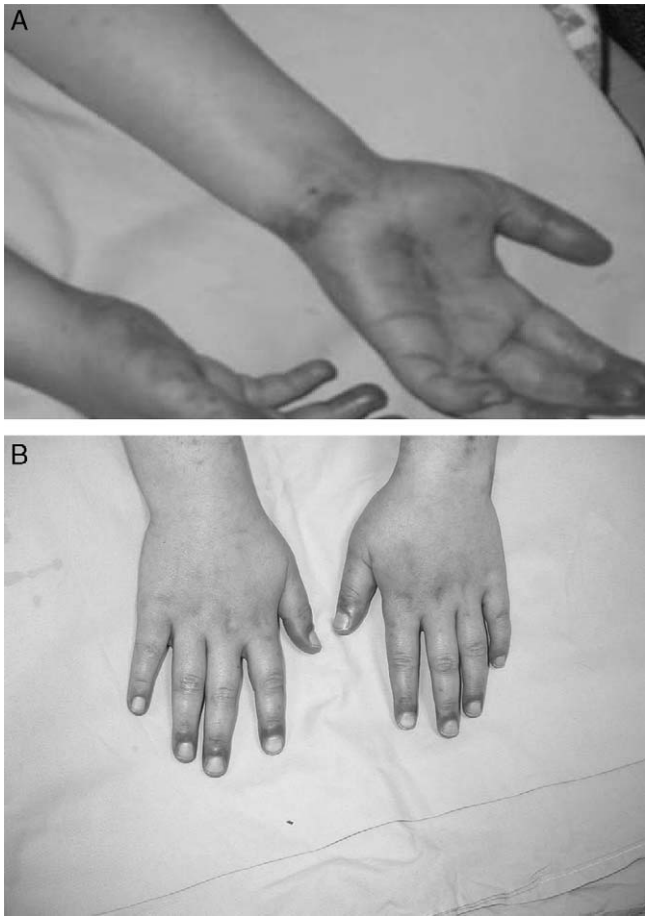

FIGURE 1. Painful erythema of the palms (A), symmetrical, edematous, painful, red, erythema developed on the hands (A, B).

DISCUSSION

The differential diagnosis of skin lesions in patients who were treated with chemotherapy are difficult because aggressive chemotherapy could change normal responses of skin and therefore, each lesion could mimic another lesion owing to different etiology. Although evaluating cancer patients who were under treatment with intensive chemotherapy, toxic epidermal necrolysis and graft versus host reactions should be kept in mind.[7] CIAE is a localized cutaneous reaction of patients with either hematologic malignancies or solid tumors to chemotherapeutic agents, and are seen in adults more commonly when compared with children.[8] The incidence varies depending on the malignancy and the chemotherapy but has been estimated to be ranging between 6% and 42%.[4] It is characterized by symmetrically well-demarcated, painful erythema of the palms and soles, which could progress to bullae formation and desquamation. The bullous variant of CIAE has been reported to be associated more frequently with cytosine arabinoside and methotrexate.[5,6] In our case, methotrexate was the suspected agent of skin reactions because it had been previously reported to cause bullous CIAE and the patient had no other chemotherapy agents other than methotrexate. Widespread distribution of lesions, like our patient, was also reported before, and the mean duration of initiation of lesions after therapy is 1 to 3 weeks.[7,8] In most instances, the lesions gradually resolve over 1 to 2 weeks with desquamation of the skin followed by reepithelization.[3] Chemotherapy-related acral erythema is generally common in adults and usually is dose dependent. Although the toxic reaction caused by chemotherapeutic agents is the suspected cause of acral erythema, the pathogenesis remains to be determined.[8,9]

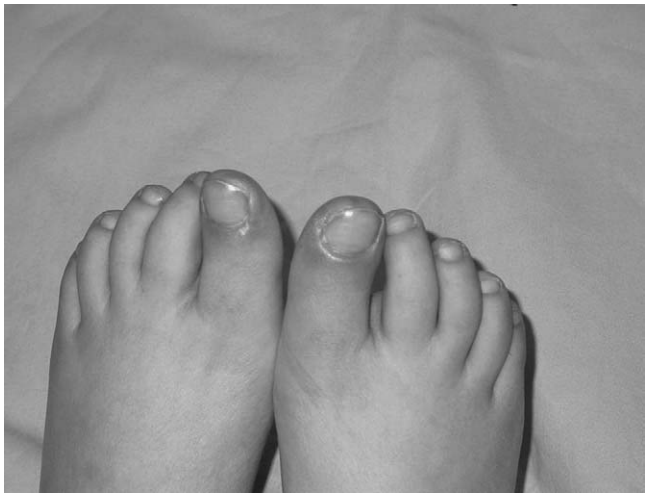

FIGURE 2. Symmetrical, edematous, painful, red, violaceous erythema developed on the both feet and the fleshy parts of the toes.

The lesions of CIAE resolve spontaneously in most patients. Therapy is generally supportive and consists of emollients and cold compresses; and topical, oral, and parenteral steroids were reported to be successful in treatment,[3,10] but these information was limited to case reports and no controlled studies were present. Our case did not respond to topical and supportive treatment and even lesions disseminated to other parts of the body.

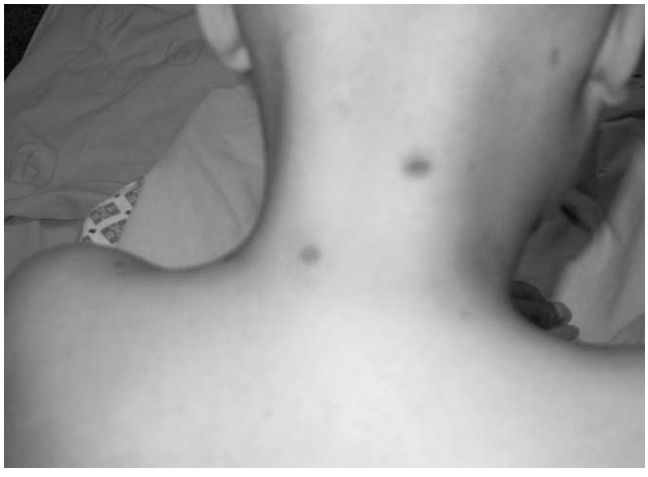

FIGURE 3. Papuler lesions on the neck.

In addition to mucosal membranes of gastrointestinal tract, perianal regions were also involved and clinicaly resulted in bloody diarrhea. Although CIAE was reported to heal spontaneously without any treatment, our patient's clinical status deteriorated and IVIG was given in addition to the supportive therapy. Although corticosteroids were reported to be useful in CIAE cases,[11,12] corticosteroid treatment was not preferred because the patient had severe neutropenia, bloody diarrhea, fever, and high risk of infection. IVIG was reported to be useful in cases with Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).[13–15] Both SJS and TEN are characterized morphologically by the rapid onset of keratinocyte cell death by apoptosis, a process that results in the separation of the epidermis from the dermis. Recent evidence supports the role for inflammatory cytokines, and the death receptor (Fas) and its ligand (FasL) in the pathogenesis of keratinocyte apoptosis during TEN. This Fas-mediated keratinocyte apoptosis is the last step culminating in epidermal detachment in TEN and could be inhibited in vitro by antagonistic monoclonal antibodies to Fas and by IVIG, which have been shown to contain natural anti-Fas antibodies.[16] Also acute graft versus host diseases show similar clinical and histopathologic features with CIAE.[12] Controlled clinical trials have shown a significant reduction in acute graft versus host diseases in patients given IVIG (500 to 1000 mg/kg) weekly after bone marrow transplantion.[17] So it could be speculated that IVIG is also effective in CIAE cases. Our patient had rapid recovery with IVIG therapy (400 mg/kg/d) for 5 consecutive days. We could not find any report of IVIG usage in CIAE cases in English literature. Because of the progression of our patient's clinical status, IVIG was chosen as the treatment choice, as IVIG was reported to be helpful in patients with TEN in which similar pathogenesis was suspected.

In conclusion, CIAE owing to methotrexate therapy is rarely seen in children. Despite the supportive therapy, our patient's clinical status progressed and responded to IVIG therapy. With this article, we want to point out that IVIG might be empirically used in the treatment of nonresponding and progressive CIAE patients.

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