

Acral erythema with bullous formation: a side effect of chemotherapy in a child with acute lymphoblastic leukemia

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SUMMARY: Aytaç S, Gümrük F, Çetin M, Tuncer M, Yetgin S. Acral erythema with bullous formation: a side effect of chemotherapy in a child with acute lymphoblastic leukemia. *Turk J Pediatr* 2010; 52: 211-214.

Chemotherapy-induced acral erythema (CIAE) with bullous formation is an uncommon complication in children. We describe herein a child who developed CIAE with bullous formation following high-dose methotrexate and cytarabine for relapsed acute lymphoblastic leukemia. The rash completely resolved within two weeks of the appearance without any specific treatment. CIAE may develop in children with hematological malignancies as a complication of pediatric chemotherapeutic regimens, and pediatricians should be aware of this phenomenon despite its rarity.

Key words: acute lymphoblastic leukemia, acral erythema, child.

Skin reactions may occur during the treatment period of malignancies and appear generally to be the complication of chemotherapeutic agents.

Chemotherapy-induced acral erythema (CIAE) has been described in patients with malignancy who have been treated with 5-fluorouracil, doxorubicin, methotrexate (MTX), mercaptopurine, and cytarabine as a single agent or in combination treatment¹. The bullous variant of this reaction has also been reported following these chemotherapeutics alone or in combination with other agents, and more frequently with cytarabine. We report a child who developed CIAE with atypical bullous formation following high-dose chemotherapy for relapsed acute lymphoblastic leukemia (ALL).

Case Report

A 12-year-old boy who was diagnosed as mixed phenotype ALL developed bone marrow relapse four months after cessation of the modified St. Jude total XIII chemotherapy protocol. The patient was treated with a BFM 95 relapsed protocol. Chemotherapy doses were administered according to the protocol with R1 regimen (dexamethasone, 6-mercaptopurine,

vincristine, MTX, cytarabine and L-asparaginase) alternating with R2 regimen (dexamethasone, 6-thioguanine, vincristine, MTX, daunorubicin, L-asparaginase and ifosfamide) with two-week intervals. According to the protocol all patients receive trimethoprim-sulfamethoxazole prophylaxis. He received the third R1 cycle that contained cytarabine and MTX. Cytarabine was given as 4 g/m² on the fifth day and MTX 1 g/m² as continuous infusion on days 1 to 3. One week after administration of the last cycle of high-dose methotrexate (HDMTX) (1 g/m²), the patient developed initially a mild pruritic and erythematous skin rash that later evolved into a painful bullous form involving the distal phalange of the thumb and hallux. Because of persistent initial symptoms including erythematous skin rash on his feet, he had received per oral sulbactam ampicillin for the suspected diagnosis of cellulites at the peripheral hospital. On the fourth day, the bullae of the feet gradually resolved and turned to a plantar desquamation, while the bullous rash of the hand increased in size. He was referred to our hospital on the fifth day of his symptoms. On admission, physical examination was normal except for erythema and bullous reaction of the hand and partial healing of the feet (Figs. 1, 2). Laboratory



Fig. 1. Erythema of the palm and extensor side bullae formation.



Fig. 2. Erythema and bullae of the sole followed by plantar desquamation.

results included hemoglobin level: 6.8 g/dl, white blood cell count: $0.4 \times 10^9/L$ and platelet count: $43 \times 10^9/L$. Despite the absence of fever, his absolute neutrophil count was below $100/mm^3$, and intravenous antibiotic was given on the fifth date of eruption and continued for the following five days. A skin biopsy was not performed because of his severe neutropenia.

The rash had almost totally resolved without corticosteroid treatment within two weeks of the appearance and reepithelialization developed without scarring. No dose reduction in chemotherapeutics was made, and there was no recurrence with the following chemotherapeutics using similar dosages.

Discussion

As described before, CIAE was seen only in patients receiving chemotherapeutic agents,

and the incidence has been estimated to range between 6% and 42%². A prodrome of dysesthesia may develop in the palms and soles, which is characteristically followed by the sudden onset of a well-demarcated, symmetrical, acute tender erythematous rash on the palms, fingers and soles, often associated with edema. The rash may become bullous and then desquamate without scarring³. Our patient's skin reaction seems similar to this description. This phenomenon is well described in adults; however, to our knowledge, pediatric cases are rare.

The exact mechanism of this reaction is unknown. Some authors cite the cumulative and high doses and the peak plasma concentration of the chemotherapeutics (5-fluorouracil, doxorubicin, cytarabine, MTX, mercaptopurine) as the reason for this phenomenon. They suggest that there might be a special immune response to the eccrine apparatus, which is present at high concentrations in the palms and soles, and in which chemotherapeutic agents may accumulate and trigger this immune response⁴. All the pediatric cases in the literature were related to HDMTX chemotherapy. Acral erythema was observed in a 13-year-old girl treated for osteosarcoma 24 hours following the seventh course of HDMTX ($12 g/m^2$), in a 3-year-old boy with relapse ALL following combination therapy containing HDMTX after 48 hours, in 3 children (15-year-old boy with ALL, 7-year-old boy with ALL and 7-year-old boy with Burkitt lymphoma) 3 to 14 days after HDMTX ($3-5 g/m^2$), in a 7-year-old boy with T-ALL receiving combination chemotherapy with HDMTX ($5 g/m^2$), and in a 12-year-old boy with osteosarcoma completing the third course of HDMTX ($12 g/m^2$)⁵⁻⁹. Nevertheless, different cases have also been reported: A 17-year-old girl with acute monoblastic leukemia developed bilateral palmar erythema and burning sensation on the fourth day of high-dose cytarabine and idarubicin treatment, which recurred one month later after high-dose cytarabine and etoposide treatment¹⁰. Additionally, CIAE with bullous reaction was described in a 12-year-old boy with B-cell lymphoma treated with a combination therapy (MTX + cytarabine)¹¹. Our case received lower doses of MTX ($1 g/m^2$) but more frequently (2-week intervals) than in the previous cases. Previous reports in adults

have indicated that skin toxicity appeared to be related to the duration of each course of cytarabine rather than the peak concentration when single high-dose cytarabine was used in refractory leukemia¹². It is unknown which agent (cytarabine, MTX or both) caused this reaction in our patient.

Histologically, vacuolar change, necrotic keratinocytes, spongiosis and epidermal atypia can be observed¹³. Immunohistochemical findings suggested that this reaction is a cell-to-cell interaction between natural killer (NK) cells and keratinocytes in the eccrine apparatus, resulting in vacuolar degeneration and spongiotic blisters with the help of cell adhesion molecules⁴. However, it was also reported that the histological features lack diagnostic specificity because they may also be seen in fixed drug eruptions and morbilliform drug reactions¹⁴. The diagnosis is based primarily on clinical suspicion and early recognition of the erythema and should be supported by skin biopsy. Although it has been implicated that there is no specific or effective treatment for CIAE since it is generally self-limited, several authors suggest corticosteroid treatment and withdrawal or reduced chemotherapy doses. Intravenous immunoglobulin therapy was also reported to be useful in cases with CIAE¹⁵.

Toxic epidermal necrolysis, bullous impetigo and bacterial skin infections such as staphylococcal skin infections should be considered in the differential diagnosis. As staphylococcal skin infections are among the most common skin diseases in children and staphylococcal scalded-skin syndrome can sometimes resemble other blistering diseases, skin biopsy can help in the differentiation. However, these disorders are usually characterized with widespread blisters, and treatment of patients with bullous impetigo or the scalded-skin syndrome usually consists of antibiotics^{16,17}. While this patient was severely neutropenic and treated with an antibiotic, bullae of the feet gradually resolved while bullous rash of the hand increased in size without widespread lesions or fever. Although skin biopsy was not available, clinical findings were identical with CIAE. We consider both cytarabine and MTX continuous infusion as the suspected agents of this complication as well as of the rare severe bullous variant form.

In conclusion, pediatricians should be aware of this phenomenon, especially in patients who are treated with multi-drug chemotherapy and HDMTX. These reactions may be heterogeneous in clinical manifestations such as in our case; bullous formation can be the main manifestation.

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