Generalized benign cutaneous reaction to cytarabine

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Background: Cytarabine-induced toxicity manifests as various cutaneous morphologies. A generalized papular purpuric eruption has not been well described.

Objectives: We aimed to characterize a distinct cytarabine-related eruption.

Methods: We reviewed all cases of cytarabine-related toxicity with papular purpuric eruptions or violaceous erythema at the University of California, San Francisco between 2006 and 2011.

Results: Sixteen cases were identified. The eruption began as erythematous papules that evolved into coalescing purpuric papules and plaques. It had affinity for intertriginous areas, neck, ears, and scalp. Pruritus was common, but no systemic complications were documented. Thirteen patients (81.3%) developed the eruption after completion of chemotherapy. Differential diagnosis often included viral exanthem (62.5%), drug eruption (50%), and vasculitis (37.5%). Histopathology was nonspecific but commonly demonstrated sparse lymphocytic infiltrates, spongiosis, and/or red cell extravasation. Importantly, the eruption was neither predicted by past cytarabine exposure nor predictive of future recurrence.

Limitations: This is a review of cases from a single institution. Observation was limited to acute hospitalization, however, charts were reviewed for subsequent reactions on rechallenge.

Conclusions: The eruption described herein represents a specific skin-limited reaction to cytarabine. Awareness of its characteristic morphology, distribution, and timeline will aid in clinical diagnosis. Reassurance concerning its benign nature will prevent unnecessary intervention or cessation of chemotherapy. (J Am Acad Dermatol 2015;73:821-8.)

Key words: cytarabine; dermatopathology; drug reactions; pathophysiology; toxic erythema of chemotherapy.

Cytarabine is a pyrimidine antagonist commonly used in the treatment of hematologic malignancies such as leukemia and non-Hodgkins lymphoma.[1-3] High doses induce cutaneous toxicity with an observed frequency ranging from 2% to 72%.[4-6] The most commonly cited cutaneous manifestations include morbilliform eruptions and acral erythema.[4,7-13] Less common reactions include neutrophilic eccrine hidradenitis,[14,15] vasculitis,[16] and eccrine squamous syringometaplasia.[17]

Although the more common cutaneous toxicities of cytarabine are well known to dermatologists and oncologists, the presentation of a papular purpuric eruption or violaceous erythema subsequent to cytarabine exposure is rarely documented in the literature.[7] Herein, we present 16 cases of these distinct cutaneous reaction patterns as part of the spectrum of cutaneous toxicities associated with cytarabine treatment. In addition, we discuss its diagnosis and prognosis.

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METHODS

We reviewed the charts of 16 patients given a diagnosis of either a papular purpuric eruption or widespread violaceous erythema secondary to cytarabine seen by the inpatient dermatology consultation service at the University of California, San Francisco between 2006 and 2011. Cases were evaluated for age, sex, timing of the cutaneous eruption, morphology, distribution of lesions, histopathology, medical history, laboratory values, interventions, and time to resolution. The Committee on Human Research (Institutional Review Board) at the University of California, San Francisco reviewed and approved this study.

Representative case report

A 68-year-old man in previously good health presented with a 2-month history of progressive weakness, fatigue, and arthralgias. He was pancytopenic. A bone-marrow biopsy specimen demonstrated features of acute biphenotypic (myeloid and B-lymphoid) leukemia. Induction chemotherapy with cytarabine (day 1-7) and daunorubicin (day 1-3) was initiated. He received an intermediate dose of cytarabine (100 mg/m^2/d for a total dose of 0.7 g/m^2). While receiving chemotherapy, he was also treated for pneumonia with vancomycin, cefepime, and moxifloxacin.

Twelve days after receiving his first dose of cytarabine, erythematous macules developed on his chest and back. These macules evolved into papules coalescing into purpuric plaques that covered the chest, abdomen, and back and extended onto the face, scalp, neck, ears, groin, and extremities (Fig 1). Lesions on the distal lower extremities resembled palpable purpura. Other than slight pruritus, the eruption was asymptomatic. The initial differential diagnosis included neutrophilic eccrine hidradenitis, Sweet syndrome, morbilliform drug eruption with secondary hemorrhage, leukocytoclastic vasculitis, leukemia cutis, and a viral exanthem with secondary hemorrhage. Two skin biopsy specimens, taken from the arm and the leg, revealed superficial hemorrhage with prominent lymphangiectases and an edematous papillary dermis and spongiotic dermatitis with extravasated erythrocytes, respectively. A diagnosis of toxic erythema of chemotherapy secondary to cytarabine was made. He was prescribed topical triamcinolone and Aquaphor (Beiersdorf Inc, Wilton CT) for symptomatic relief. Eighteen days after his first exposure to cytarabine, dry desquamation was noted, with continued resolution of the eruption upon discharge 26 days after initial exposure.

CAPSULE SUMMARY

- A generalized papular purpuric eruption is a cutaneous reaction pattern specific to cytarabine.
- Lesions may mimic cutaneous vasculitis or neutrophilic diseases but presence of lesions in intertriginous areas, posterior neck, and ears are clinical clues.
- This reaction to cytarabine is benign, self-limited, and may present after the completion of the course of cytarabine.

RESULTS

Clinical features

Clinical features of our patients are summarized in Table I. No gender or age predominance was noted in our cohort other than that reflective of leukemia and lymphoma. Of the patients presenting with cutaneous chemotherapy toxicity, 13 (81.3%) received high-dose cytarabine ($\geq$1 g/m^2/d). Duration of treatment with cytarabine ranged from 2 to 7 days. The first skin lesions were documented an average of 8.6 days after first exposure to cytarabine. Of note, 13 patients (81.3%) did not develop the cutaneous eruption until after the completion of chemotherapy.

Initial improvement was observed in all patients before discharge. Clearance and desquamation were first noted 6 to 20 days after cytarabine exposure, with an average of 15.2 days after cytarabine exposure. One eruption was noted to be completely cleared within 19 days whereas the longest documented eruption continued for 30 days after first cytarabine exposure. Because many patients were discharged before complete resolution of the eruption, we were unable to clearly determine time to complete resolution in all patients.

Morphology

Table II and Figs 1 and 2 show the initial and dominant morphologies of the cytarabine papular purpuric eruption. Notice that most eruptions evolved significantly, initially appearing as erythematous papules and then evolving toward purpuric papules. Of note, although 14 patients developed purpuric lesions, 6 of the patients (37.5%) developed purpura only in the dependent lower extremities.

Lesions of the papular purpuric eruption typically originated on the upper and lower extremities, chest, and axilla (Table III). The most common areas involved were the abdomen and lower extremities (both present in 93.8% of patients). Other affected areas included the upper extremities, chest, and back.