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Single Case

Bilateral Ear Swelling and Erythema after Chemotherapy: A Case Report of Ara-C Ears

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Keywords
Cytarabine · Ear rash · Cutaneous adverse effects · Drug eruption

Abstract
Cytarabine is an antimetabolite commonly used to treat hematological malignancies, especially acute myeloid leukemia (AML), acute lymphoblastic leukemia, and non-Hodgkin's lymphoma. Cytarabine-induced cutaneous adverse effects are common, usually manifesting as morbilliform eruptions predominantly on the acral site, intertriginous zone, and to a lesser extent on the elbows, knees, neck, and ears. The presentation on ears is usually called “Ara-C ears,” which is considered as a rare subtype of acral erythema. We report a 53-year-old Thai woman with AML who developed cytarabine-induced rashes. The lesions began on symmetrical bilateral ears, posterior auricular areas, and forehead followed by expansion to the trunk and extremities. The clinical presentations and histopathological findings were compatible with toxic erythema of chemotherapy. After giving cetirizine 10 mg orally twice daily and 0.1% triamcinolone acetonide cream twice daily, the lesions gradually improved over 10 days. Notably, two additional courses of high-dose cytarabine were administered without any recurrence.

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Introduction

Cytarabine or cytosine arabinoside, also known as Ara-C, is a pyrimidine antagonist used for the treatment of hematologic malignancies including acute myeloid leukemia (AML), lymphoblastic leukemia, and non-Hodgkin’s lymphoma [1]. It is an antimetabolite antineoplastic agent that inhibits S-phase of the cell cycle during DNA synthesis. Most of the cytarabine-induced cutaneous adverse effects are delayed-type hypersensitivity reactions occurring 1–2 weeks after drug administration [2]. Common cutaneous reactions include morbilliform eruptions and toxic erythema – manifesting as painful erythematous patches or edematous plaques on the acral site, intertriginous zone, and less frequently on the elbow, knees, neck, and ears [3]. The presentation involving the pinnae of the ears is commonly referred to as “Ara-C ears” [4], which is categorized as a rare subtype of acral erythema. There is no clear evidence whether this is a dose-dependent cutaneous adverse reaction or not, since the reaction has been reported in the patients treated with low- as well as high-dose Ara-C [2, 5]. Most cleared spontaneously without requiring treatment. Additionally, complications are rarely reported and re-challenging is safe. Therefore, the definitive diagnosis is essential to prevent discontinuation of chemotherapy. We report a patient with AML presenting with Ara-C ears after the first exposure and later achieving stable disease upon re-challenge without any recurrence.

Case Report

A 53-year-old Thai woman presented with significant weight loss and ecchymoses. The complete blood count showed bicytopenia with presence of promyelocyte and myeloblast. Bone marrow evaluation revealed 30% of blast cells which were positive for CD34. She was later diagnosed with AML with the biallelic mutations of the CCAAT/enhancer binding protein α (CEBPA) gene. Induction chemotherapy which was composed of cytarabine 160 mg per day (100 mg/m²/dose, days 1 to 7) and idarubicin 19 mg per day (12 mg/m²/dose, days 1 to 3) was administered. On the 6th day of chemotherapy administration, she developed itchy, non-sclary skin eruptions on the forehead, both ears, and posterior auricular areas. The lesions gradually progressed to other regions of her body (i.e., trunk, arms, legs) without mucosal or palmoplantar involvement (Fig. 1).

Dermatologic examination showed multiple itchy, partially blanchable erythematous to dusky red papules coalescing into plaques and petechiae on the forehead, both ears, and posterior auricular area (Fig. 1). Similar lesions were observed on the trunk and extremities. The remaining examinations were unremarkable.

The histopathological findings revealed superficial perivascular and perifollicular cell infiltration and absence of perieccrine infiltration, vacuolar alteration of basal cell layer, and scattered necrotic keratinocytes in the epidermis. Inflammatory cell infiltration was mainly composed of lymphocytes, with few eosinophils, and rare scattered necrotic keratinocytes (Fig. 2). These findings were consistent with the diagnosis of toxic erythema of chemotherapy.

Following the diagnosis, she was treated with cetirizine 10 mg orally twice daily and application of 0.1% triamcinolone acetonide cream twice daily. At day 10 follow-up, the lesions gradually improved. The rashes resolved with post-inflammatory erythematous to brownish patches (Fig. 3). At 1 month follow-up, all lesions had complete resolution without scar formation. The patient was then treated with high-dose cytarabine of 3 g per day (2 g/m²/dose) for an additional two cycles without any recurrence of cutaneous adverse reactions.
Discussion

We report a rare case presentation of Ara-C ears, which is a variant of toxic erythema of chemotherapy. She developed itchy, non-scaly skin eruptions on the forehead, both ears, and posterior auricular areas after being given cytarabine. The comprehensive clinical data including characteristic morphology, distribution, and drug exposure timeline confirmed the diagnosis. Toxic erythema of chemotherapy, including Ara-C ears, commonly appears 2 days to 3 weeks after giving chemotherapeutic agents [3, 4]. Thus, cytarabine is considered to be the most likely drug responsible for these rashes since a temporal relationship between clinical features and the administration of specific drugs is apparent. Moreover, the rashes remarkably disappeared, on the tenth day, after this culprit drug had no longer been administered. The histopathological findings excluded other possible causes – leukocytoclastic vasculitis, Sweet syndrome, leukemia cutis, or disseminated infection. The histopathology features of cytarabine-induced toxic erythema commonly reveals sparse lymphocytic infiltrates, spongiosis, red cell extravasation, and dysmaturation [6]. Ruben et al. [2] reported that spongiotic dermatitis was found in 33%, followed by perivascular dermatitis, sparse neutrophilic dermatitis, and subepidermal vesiculation with epidermal necrosis. As the histopathological findings were non-specific, the diagnosis of toxic erythema of chemotherapy secondary to cytarabine therefore remains largely a clinical diagnosis.

Cytarabine is a synthetic analog of nucleoside cytidine, which is used alone or in combination with other antineoplastic drugs to treat hematological malignancies, especially AML and acute lymphoblastic leukemia [1]. Although it is one of the most effective drugs for the treatment of AML, systemic adverse reactions including myelosuppression, central nervous system complications, hepatic dysfunction, nausea, vomiting, and thrombophlebitis occur frequently [7]. In addition, several cutaneous adverse events from cytarabine have been reported – particularly at high doses – ranging from 39 to 55% of patients [5, 8, 9]. The most common cutaneous presentations include morbilliform eruption and toxic erythema of chemotherapy [9, 10], which includes acral erythema (also known as palmar-plantar erythrodysesthesia) [3], eccrine abnormalities (e.g., neutrophilic eccrine hidradenitis and eccrine squamous syringometaplasia) [9, 11], and inflammatory seborrhoeic keratosis [12]. The variable cutaneous manifestations of cytarabine-induced skin toxicity may be attributed to polymorphisms in the genes involving in the drug metabolism [13].

The clear pathogenesis of the dermatologic adverse reactions has not been well established; however, they may be associated to cellular damage of the epidermis, eccrine sweat glands, and ducts from direct toxic effect of the chemotherapeutic agent [3]. Additionally, hypersensitivity reaction is one of the plausible mechanisms that might be ascribed to the cutaneous toxicities of cytarabine [10]. The mostly affected sites are the acral and intertriginous areas, which are related to the high density of eccrine glands and sweating [3, 14]. Grille et al. [8] revealed that of 46 AML patients who were treated with cytarabine, cutaneous adverse reactions occurred in 39% of such individuals. The distribution was diffuse (52%), localized to acral (39.3%) and flexural areas (8.7%). The reactions were observed from 2–8 days post-chemotherapy.

The eccrine glands are not only found at acral sites but also at forehead, ears, elbows, and knees – despite the lower density [3, 15]. This could account for the unusual distribution of the rash in our patient, who presented with lesions on the forehead and bilateral ears, later spreading to the trunk with palmo-plantar sparing. Ruben et al. [2] and Krulder et al. [16] also reported this ear involvement as a relatively rare condition. Despite reported studies, its pathophysiology is poorly understood to date. Further studies will need to be undertaken to unveil
this particular mechanism. Our patient’s cutaneous lesions developed on day 6 after the first chemotherapy administration. This is consistent with the previous study, reported by Ruben et al. [2], which revealed that lesions were documented an average of 8.6 days after first exposure to cytarabine. The cutaneous reactions developed without age or gender predilection [2]. In spite of that, the skin eruption occurs more frequently with high-dose regimen [2, 9]. Interestingly, patients who presented with exanthema after the first cycle had recurrence after repeated cytarabine exposure of only 27–33.3% [8, 9]. Likewise, our patient did not present with any cutaneous eruptions after subsequent exposure. Thus, our report confirms results of the previous study and reinforces that drug discontinuation or dose reduction is unnecessary, and re-challenge is safe.

For our patient, all cutaneous eruptions improved within 10 days and completely resolved in 30 days. Similarly, Ruben et al. [2] revealed that the average time of clearance and desquamation is 15 days and the complete resolution was observed within 30 days. Moreover, extensive testing and/or treatment could be spared [2, 3, 8, 17]. Only symptomatic treatment with cold compression, analgesics, and oral antihistamine is required for particular cases. Most eruptions resolve without any sequelae [9, 17].

**Conclusion**

We report an AML patient with cytarabine-induced cutaneous adverse reaction that began at the forehead and bilateral ears before spreading to trunk and extremities with acral sparing. Only a minority of patients experience the recurrence of this adverse cutaneous reaction after re-exposure. Because of the benign and self-limited nature, dose decrement or discontinuation is not necessary for patients with skin-limited disease.

**Statement of Ethics**

The authors have no ethical conflicts to disclose. The patient has given written informed consent to publish her case.

**Disclosure Statement**

The authors have no conflicts of interest to disclose. P.J. collected the data and wrote the initial manuscript draft. And K.C. evaluated, revised the manuscript, and acted as the corresponding author. All authors provided critical feedback and contributed to the final version of the manuscript.
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Fig. 1. Multiple itchy, partially blanchable erythematous to dusky red papules coalescing into plaques and petechiae on both ears and posterior auricular areas.

Fig. 2. Histopathological findings demonstrate superficial perivascular and perifollicular cell infiltration (a), some areas with basal vacuolization (b), and inflammatory cell infiltrated, mainly composed of lymphocyte, some eosinophils, associated with few scatter necrotic keratinocytes (c).
Fig. 3. Resolution of skin lesions on the forehead, both ears, and posterior auricular areas at the follow-up visit on day 10.