ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 04 | April - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

UNEXPECTED SIDE EFFECT OF CYTARABINE – A CASE OF AURICULAR ERYTHEMA – CASE REPORT AND REVIEW OF LITERATURE

Hematology

Dr. Rudresha A. H. DM Medical Oncology, Associate Professor, Kidwai Memorial Institute of Oncology.
Dr. Sankalp Jagga* MD General Medicine, Senior Resident -1 in DM Medical Oncology, Kidwai Memorial Institute of Oncology. *Corresponding Aurthor
Dr. Animesh Gupta MD General Medicine, senior resident-3 in DM Medical Oncology.
Dr. Suresh Babu DM Medical Oncology, Professor, Kidwai memorial institute of oncology.
Dr. KN Lokesh DM Medical Oncology, Associate Professor, Kidwai memorial institute of oncology.
Dr. LK Rajeev DM Medical Oncology, Associate Professor, Kidwai memorial institute of oncology.
Dr. Smitha Saldanha DM Medical Oncology, Associate Professor, Kidwai memorial institute of oncology.
Dr. Linu Jacob DM Medical Oncology, Professor, Kidwai memorial institute of oncology

ABSTRACT

A 19-year-old female with acute myeloid leukemia (AML) developed red ear syndrome (RES) after initiating cytarabine chemotherapy. On day 9, she experienced erythema, swelling, and itching of the external ears. Physical examination revealed bilateral ear redness, facial edema, and erythematous papules on the upper limbs, with a differential diagnosis of drug-induced rash and catheter-induced thrombosis. Blood tests indicated pancytopenia, but renal and liver function remained normal. Doppler evaluation showed a right cephalic vein thrombus, but no major vessel involvement was found. Cytarabine-induced acral erythema, particularly RES, was suspected. The patient received low-dose corticosteroids (prednisolone) and antihistamines (cetirizine), leading to symptom relief and complete resolution of the ear erythema by day 20. This case highlights the rarity of cytarabine-induced RES and emphasizes the need for early identification and treatment of cutaneous toxicities during chemotherapy for AML. Prompt intervention with corticosteroids and antihistamines can provide effective symptom management. This report contributes to a better understanding of the dermatologic side effects of cytarabine, particularly RES, in AML treatment.

KEYWORDS

CYTARABINE, ACUTE MYELOID LEUKEMIA (AML), RED EAR SYNDROME, AURICULAR ERYTHEMA

INTRODUCTION

Cytarabine, a pyrimidine antagonist commonly referred to as cytosine arabinoside or Ara-C, is used to treat hematologic malignancies such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma.[1] It is an antimetabolite agent that prevents DNA synthesis by blocking the S-phase of the cell cycle. One to two weeks following the administration of medication, delayed-type hypersensitivity responses account for the majority of cytarabine-induced cutaneous side effects. [2] Morbilliform eruptions and toxic erythema are frequent dermatologic reactions, manifesting as painful erythematous patches or swollen plaques. These are most commonly seen in acral areas and intertriginous zones, with less frequent involvement of the elbows, knees, neck, and ears. [3] This presentation involving the ear pinnae is sometimes called "Ara-C ears". [4] Cytarabine-induced auricular erythema, an uncommon subtype of acral erythema, is depicted in this study as an example.

CASE REPORT

A 19-year-old female presented to the emergency department with fatigue and fever persisting for 15 days. Laboratory evaluations are depicted in Table 1, The peripheral smear revealed normocytic, normochromic anemia, thrombocytopenia, and a left-shifted myeloid series. This series shows 30% large to medium-sized blasts with prominent nucleoli, fine chromatin, and basophilic cytoplasm, suggesting acute myeloid leukemia (AML). Bone marrow aspiration and flow cytometry demonstrated a hypercellular marrow with 40% medium to large-sized blasts. These blasts were positive for HLA-DR, CD-34, MPO, CD13, CD33, CD117, CD64, and aberrant CD19, which confirms the diagnosis of acute myeloid leukemia. The cytogenetic analysis revealed a t(8;21)(q22;q22) translocation, and the AML PCR panel was positive for the AML1-ETO fusion transcript, indicative of a favorable risk profile. The patient was initiated on a standard 3+7 induction chemotherapy regimen, consisting of daunorubicin (60 mg/m² over 2 hours from days 1 to 3) and cytarabine (100 mg/m² as a 24-hour continuous infusion from days 1 to 7). She also received prophylactic ciprofloxacin and voriconazole, along with supportive care. On day 9 of therapy, the patient reported itching and redness of both external ears, with no fever or chills (Figure 1.a). Physical examination revealed significant erythema of the ears, facial edema, multiple red papules on both upper limbs, and swelling of the right arm at the site of the peripherally inserted central catheter (PICC) line. Differential diagnoses of drug-induced rash and catheter-induced thrombosis were kept. For evaluation, blood investigations revealed pancytopenia on the CBC, while both renal function tests (RFT) and liver function tests (LFT) were within normal limits, doppler of the right arm was suggestive of right cephalic vein thrombus, and computed tomography pulmonary and major vessel angiogram was done which was normal and SVC (Superior Vena Cava) thrombosis was also ruled out. A dermatologist's opinion was taken, and Cytarabine-induced acral erythema was suspected. The patient was started on low-dose oral prednisolone (20 mg daily for the first 5 days and 10mg daily for the next 5 days) and tablet cetirizine (10 mg daily). By day 20 of induction therapy, she showed significant clinical improvement in itching and ear redness (Figure 1.b).

DISCUSSION

Ara-C, an antimetabolite agent, is commonly used in many hemato-oncological conditions. Therefore, it is critical to understand its adverse effects to ensure timely diagnosis and suitable treatment. The Ara-C syndrome refers to a group of symptoms that include fever, bone pain, myalgias, maculopapular rash, conjunctivitis, and chest discomfort. Prophylactic steroids may be able to avoid this syndrome.[5] Ara-C-related skin toxicity is commonly associated with high-dose Ara-C treatment. One study reported that it occurred in 53% of cases.[6] Although the precise etiology of dermatologic adverse responses is unclear, the direct toxic effect of chemotherapeutic drugs may be responsible for cellular damage to the epidermis, eccrine sweat glands, and ducts.[7]

Furthermore, one of the likely pathways that could be linked to cytarabine's cutaneous toxicities is hypersensitivity reaction. [8] A case report by Friedman et al. (2007) presents a rare manifestation of cytarabine-induced red ear syndrome in a patient with acute myeloid leukemia. The study demonstrated that high-dose cytarabine (3g/m²) can induce bilateral ear redness, swelling, and warmth, which were reversible with supportive care within 72 hours. Furthermore, re-challenge with a reduced dose of cytarabine (1.5g/m²) did not result in recurrence, emphasizing the importance of careful dose titration.[9] The primary forms of treatment are topical or oral corticosteroids, antihistamines, and supportive measures like cold compresses.[10]

CONCLUSION

This case underscores the importance of recognizing red ear syndrome as a potential side effect of cytarabine in the context of acute myeloid leukemia treatment. The patient's symptoms of bilateral ear erythema and itching were effectively managed with corticosteroids, resulting in significant improvement. This highlights the necessity for vigilant monitoring of skin reactions during chemotherapy to ensure timely intervention and enhance patient care.

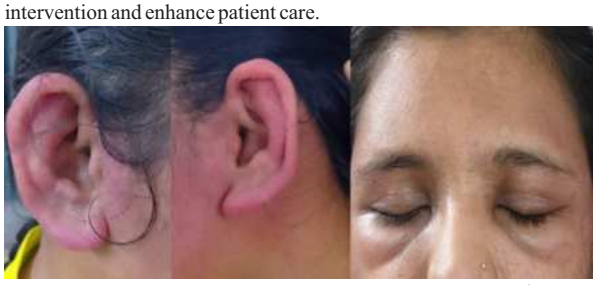

Figure 1.a bilateral red ear and periorbital puffiness on the 9th day of induction therapy

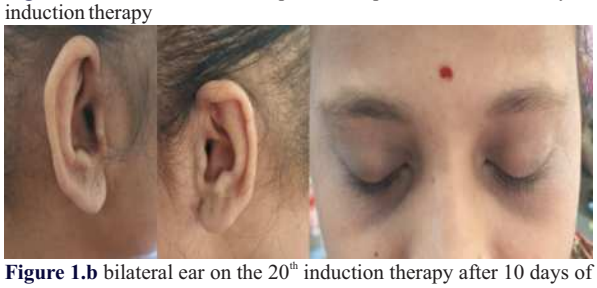

Figure 1.b bilateral ear on the 20th induction therapy after 10 days of corticosteroids and complete resolution of redness

Table 1: Blood Investigations At Presentation

CBC (complete blood count)	
Hb	8 g/dl
TLC (total leukocyte count)	5260 cells/µL
Blast %/N%/Band% /L%/M%/E%/Baso%	30%/20%/15%/10%/5%/2%/1%
Platelet count	11,000 cells/µL
PCV	24.3%
RFT (renal function test)	
Serum Creatinine /BUN	0.8 mg/dl / 6 mg/dL
LFT (liver function test)	
Total Bilirubin	0.40 mg/dL
Total Protein	7 g/dL
ALBUMIN / GLOBULIN	3.8 g/dL / 3.2g/dL
Alkaline Phosphatase	63 U/L
SGOT /SGPT	16 U/L /18U/L

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