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Pigmentation of the Tongue, Nails, and Gingiva Following Adriamycin Therapy: A Literature Review and Clinical Insights

Aslı Geçgel[1]*, Oğuzcan Özkan[1], Fatma Pınar Açar[1] ,Burçak Karaca[1], Erdem Göker[1]

1 Ege University, Faculty of Medicine, Dept. of Medical Oncology, İzmir, Türkiye

*** Corresponding Author**: Aslı Geçgel **E-mail:** dr.asltrgt@gmail.com

ABSTRACT

Objective: Hyperpigmentation in the mucosa of the tongue and mouth may also occur with the administration of combination chemotherapy containing doxorubicin (Adriamycin). Chemotherapeutic agents may occasionally necessitate discontinuation, either temporarily or permanently, despite the fact that most of these side effects are purely cosmetic and resolve following treatment. The return of nail growth and coloration a few weeks or months after therapy cessation suggests the involvement of chemotherapeutic drugs. Following Adriamycin administration, pigmentation observed in the tongue, nails, and oral mucosa typically diminishes upon discontinuation of the medication without the need for additional treatment. However, careful monitoring is essential to ensure that no alternative explanations are overlooked.

Conclusion: To enhance awareness and facilitate the exchange of experiences regarding the management of this rare side effect, we present four cases of patients who developed nail, oral mucosa, and gingiva pigmentation following combination therapy with Adriamycin and cyclophosphamide in our clinic.

Keywords: adriamycin, hyperpigmentation, chemotherapy, side effects, nail, tongue, oral mucosa

INTRODUCTION

One relatively uncommon cutaneous side effect of chemotherapy drugs is nail toxicity. Despite the fact that most of these side effects are merely cosmetic and resolve following treatment, chemotherapeutic medications may occasionally necessitate discontinuation, either temporarily or permanently (1).

Hyperpigmentation in the mucosa of the tongue and oral mucosa may also occur with the administration of combination chemotherapy containing doxorubicin (Adriamycin).

Chemotherapeutic drugs' antimitotic action readily targets the constantly dividing nail matrix cells and oral mucosal cells (2). The mechanism of pigmentation remains unknown. The return of nail growth and coloration a few weeks or months after therapy cessation suggests the involvement of chemotherapeutic drugs (3).

To enhance awareness and facilitate the exchange of experiences regarding the management of this uncommon side effect, we present four cases of patients who developed nail, oral mucosa, and gingiva pigmentation following combination therapy with Adriamycin and cyclophosphamide in our clinic.

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CASE SERIES

Case 1:

A 37-year-old female patient presented to the hospital with a palpable mass in her left breast. Mammography revealed a 24*19 mm spiculated contoured Birads 5 mass at the periphery of the left breast. Trucut biopsy pathology confirmed invasive ductal carcinoma. In January 2023, she underwent a sentinel lymph node biopsy (SLNB) and partial mastectomy. Pathology results showed a 3 cm tumor, CerbB-2 negative, 80% (2+) estrogen receptor (ER), 35% Ki67, and 60% (2+) progesterone receptor (PR). Sentinel lymph nodes were reactive. Surgical margins were clear of tumor cells. Adjuvant chemotherapy was initiated due to the elevated Ki67 to reduce the risk of recurrence. The patient received four cycles of dose-dense Adriamycin+cyclophosphamide (ddAC) followed by four cycles of dose-dense paclitaxel. During her visit for the third course of ddAC, the patient presented with small, dark-colored macules on the edges of her tongue, dark pigmentation in her upper and lower gums, and bilateral nail bed pigmentation on her fingers and toes (Figure 1). Blood pressure and vital signs were normal, and biochemical measurements did not show any abnormalities. Evaluation for adrenal insufficiency revealed normal cortisol and ACTH levels, and thyroid function tests were within normal limits. Apart from chemotherapy, no other medications were implicated in the onset of these symptoms. Treatment continued under the assumption that the lesions were related to Adriamycin administration.

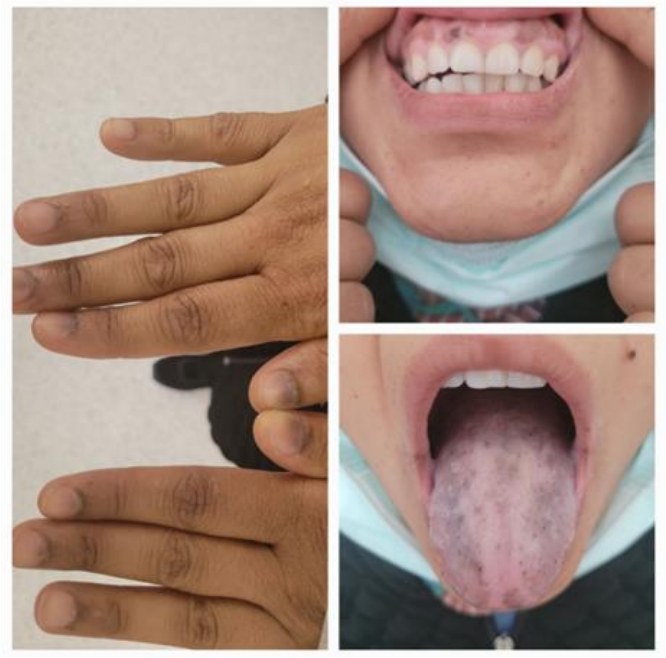

Figure 1. Figure 1. Pigmentation of tongue, upper and lower gingiva and upper extremity nails (case 1)

Case 2:

A 43-year-old woman presented to the hospital with complaints of hardness in her right breast. Mammography revealed hypermetabolic metastatic lymph nodes in the right axillary area and a soft tissue lesion in the upper inner-upper outer quadrant of the right breast, extending throughout the breast's parenchyma without a clear nodular pattern. Breast trucut biopsy results showed 20% Ki67, 80% PR (3+), 90% ER (3+), and CerbB-2 negative invasive ductal carcinoma. Malignant cytology was confirmed from a fine needle aspiration biopsy (FNAB) performed on the right axillary lymph node. The patient was scheduled to receive neoadjuvant chemotherapy consisting of 4 cycles of ddAC and 12 weeks of paclitaxel. Upon arrival for the fourth cycle of ddAC, black discoloration localized in the nail beds of the patient's bilateral fingernails was observed (Figure 2). No visible pigmentation was noted in any other area of her body. Biochemical tests were within normal limits, and vital signs were normal. Doxorubicin was considered the primary cause of the pigmentation. Her medical management continued accordingly.

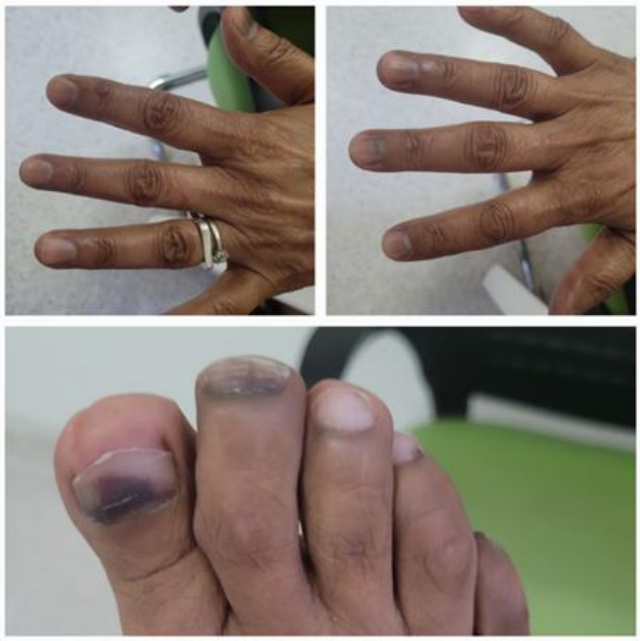

Figure 2. Black pigmentation on bilateral lower and upper extremity nails (case 2)

Case 3:

A 72-year-old female patient presented with a palpable lump in her left breast. Mammography revealed a 16 mm mass lesion with irregular outlines in the upper outer quadrant of the left breast. No lymphadenopathy was observed in the axillary region on breast ultrasonography. Trucut biopsy confirmed invasive ductal carcinoma along with ductal carcinoma in situ; PR was 100% (3+), Ki67 was 15%, ER was 100% (3+), and CerbB-2 was negative. In May 2023, the patient underwent partial mastectomy and SLNB. Histological analysis revealed hormone-positive, HER2-negative invasive ductal carcinoma and one metastasis to an axillary nonsentinel lymph node. Adjuvant chemotherapy was initiated, consisting of 4 cycles of ddAC followed by 12 weeks of paclitaxel. Brown-black pigmentation was observed in the bilateral fingernail beds during the fourth cycle of ddAC (Figure 3). No pigmentation was noted in other parts of her body. Vital signs and blood biochemistry parameters were normal. Paclitaxel therapy was continued. The pigmentation resolved upon completion of treatment, as confirmed during follow-up appointments.

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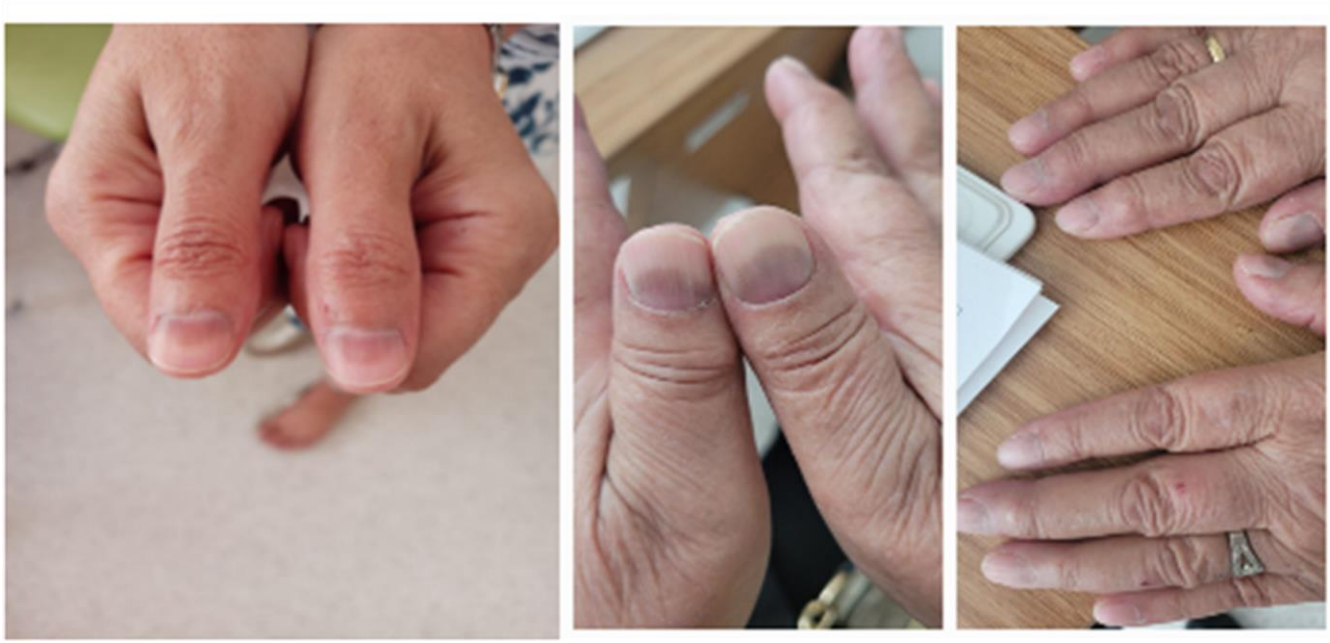

Figure 3. Brown-black discoloration of bilateral upper extremity nail beds (case 3); Black pigmentation of bilateral upper extremity nail beds (case 4)

Case 4:

A 73-year-old woman presented after discovering a lump in her right breast. Mammography revealed numerous pathological lymphadenopathies in the right axilla and an irregularly bounded nodular opacity, measuring 18 mm, in the upper middle quadrant of the right breast. Breast tru-cut biopsy confirmed glycogen-rich invasive apocrine carcinoma; CerbB-2, ER, and PR were negative, while Ki67 was 20%. Fine needle aspiration biopsy of the right axillary lymph node showed benign cytology. PET/CT showed no evidence of distant metastases. In July 2023, the patient underwent right partial mastectomy and SLNB. Pathology revealed grade 2 invasive ductal carcinoma plus ductal carcinoma in situ (high grade), measuring 15 mm, with extranodal dissemination (right sentinel lymph node sample) and carcinoma metastases in 2 out of 5 lymph nodes; ER, PR, and CerbB2 were 10% (2+), and Ki67 was 25%. HER2 FISH tests yielded negative results. Adjuvant chemotherapy consisting of 4 cycles of ddAC followed by paclitaxel for 12 weeks was scheduled for the patient with T1N1M0. By the end of the fourth treatment visit, intense, nearly black pigmentation was observed in all nail beds, particularly in the bilateral thumb nails (Figure 4). No pigmentation was noted in any other area of the patient's body. Vital signs and biochemical markers remained stable. Therapy was continued accordingly.

DISCUSSION

Breast cancer stands as the most prevalent illness affecting women globally, a multifactorial condition influenced by both genetic and environmental factors, and remains the leading cause of cancer-related mortality (1). Adriamycin and cyclophosphamide combination are commonly employed chemotherapeutic agents in neoadjuvant, adjuvant, and metastatic stages of breast cancer treatment (4, 5). Nail abnormalities induced by medications can manifest a wide array of clinical symptoms, many of which are dose-dependent and resolve upon discontinuation of the drug (6).

Nail changes and hyperpigmentation have been documented following cytotoxic chemotherapy (such as doxorubicin, cyclophosphamide, fluorouracil, docetaxel) and tyrosine kinase inhibitors like gefitinib. Additionally, hyperpigmentation can manifest in the mucosa and tongue (7).

While some nail modifications may cause discomfort and affect appearance, others can be painful and impede daily activities or mobility (8). Certain side effects, apart from purely cosmetic ones, may necessitate alterations in chemotherapy regimens.

In a study involving 205 patients, diffuse nail hyperpigmentation emerged as the most common side effect with the combination of cyclophosphamide and adriamycin (1). A prospective cohort study evaluating the toxicity profile of 146 breast cancer patients receiving paclitaxel following ddAC revealed skin hyperpigmentation in 96.6% of the patients (9). The FAC and AC-P regimens are widely utilized in breast carcinoma treatment. A comparative study showed hyperpigmentation development in 49 patients receiving the FAC regimen compared to only one patient on the AC-P regimen (10). Taxanes and anthracyclines therapy, such as doxorubicin, may result in painful onycholysis and subungual abscesses in the skin (11). Although the exact pathophysiology remains unclear, several chemotherapy drugs, including doxorubicin, may elevate melanocyte-stimulating hormone (MSH) levels, potentially explaining why this side effect is more prevalent in individuals with darker skin tones (12). Pigmentation observed in the tongue, nails, and oral mucosa typically regresses following cessation of Adriamycin without requiring additional treatment (6). Numerous case reports and case series have documented this type of hyperpigmentation, which tends to resolve weeks to months after discontinuation of doxorubicin (13). However, vigilant observation is essential to ensure that alternative explanations are not overlooked.

CONCLUSION

Recognized side effects of anticancer drugs may necessitate dose adjustments or discontinuation, potentially compromising their efficacy. Hence, ongoing research endeavors should explore novel treatments or combinations that can deliver high response rates while mitigating the frequency and severity of side effects.

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Author Contributions: AG, OO, FPA, BK, EG: Designed and directed the study, Literature search, Data collection, Statistics **AG:** Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee. Informed consent was obtained from all participants of this study.

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