BRIEF ARTICLES

Why is My Skin Turning Black? A Rare Side Effect of Capecitabine

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ABSTRACT

Introduction: Capecitabine is an oral chemotherapy frequently used in the treatment of metastatic breast and colorectal cancers. Drug-induced cutaneous hyperpigmentation is a rare adverse effect of capecitabine, which is almost exclusively reported with development of hand-foot syndrome (HFS). Here, we report a case of capecitabine-induced hyperpigmentation affecting the hands, feet, face, and tongue in the complete absence of HFS.

Case report: An 82-year old man presented with progressive hyperpigmentation of his hands, feet, face, and tongue shortly after initiating capecitabine for treatment of colon adenocarcinoma. There was no associated erythema, edema, blistering, desquamation, tingling, or tenderness. After completion of capecitabine therapy, he endorsed 95% resolution of all hyperpigmentation.

Discussion: Previous reports of capecitabine-induced hyperpigmentation have argued that it may be a sign of impending toxicity and should be a part of the HFS grading scale. Others argue that the two are separate entities, yet the mechanism is still unknown. This case supports that capecitabine can cause hyperpigmentation independent of HFS, and thus, should be evaluated as a separate entity of HFS if other symptoms are lacking.

INTRODUCTION

Capecitabine is an oral chemotherapy prodrug of 5-fluorouracil (5-FU) widely used in metastatic breast cancer and colorectal cancer treatment. Capecitabine has an array of side effects, but the most common and potentially disabling is hand-foot syndrome (HFS), also called palmo-plantar erythrodysesthesia. Few cases of capecitabine-induced hyperpigmentation have been reported, almost all of which were associated with HFS. We present a case of capecitabine-induced hyperpigmentation independent of HFS.

CASE REPORT

An 82-year-old African American man presented for darkening of his hands, feet, and face after beginning adjuvant

chemotherapy with capecitabine for colon adenocarcinoma. One to two weeks after starting therapy, he developed a prominent darkening of his palms and soles, which he was unable to remove with vigorous washing. The darkening was progressive, with a predilection for skin creases. Within another week, he experienced similar generalized darkening on his face despite routine use of sunscreen. He also began to see multiple new "moles" under his eyes on a regular basis. He denied any associated redness, burning, blistering, tenderness, numbness, tingling, or other discomfort associated with the discoloration in the affected areas.

His face had poorly-defined hyperpigmented patches, predominantly in the beard distribution along with scattered hyperpigmented macules below his eyes (Figure 1). On the anterolateral aspects of his tongue were poorly-defined, mildly hyperpigmented gray/blue macules (Figure 1). There were ill-defined darkly hyperpigmented patches on his palms and soles with accentuation in the palmar creases (Figure 2). There was no associated erythema, edema, blistering, lichenification, desquamation, or tenderness with any of the lesions. The patient was counseled that this type of hyperpigmentation is a potential side effect of capecitabine therapy and would likely persist while he is on medication. After completing therapy, the hyperpigmentation slowly faded back to his normal skin tone. At approximately 10 months after discontinuation of capecitabine, he endorsed a 95% resolution of all hyperpigmentation.

DISCUSSION

Capecitabine is an oral antineoplastic agent converted to 5-fluorouracil (5-FU) by thymidine phosphorylase.[1] 5-FU and its derivatives have been associated with various types of hyperpigmentation, which occurs in up to 5% of patients;[2-3] however, the mechanism remains largely unknown. Previously reported patterns of hyperpigmentation include supravenous serpentine eruptions after peripheral venous administration of 5-FU[2] and eruptive lentiginosis of the palms and soles.[3] However, the most common cutaneous side effect of capecitabine is hand-foot syndrome (HFS), which manifests as dysesthesias and erythema that can progress to swelling, blisters, desquamation, and pain on the hands and feet.[4] Our patient presented with asymptomatic, rapid-onset hyperpigmentation involving the face, tongue, palms, and soles shortly after beginning capecitabine. While hyperpigmentation of acral skin is occasionally seen in association with HFS, it has very rarely been reported as an isolated side effect of capecitabine, especially with such robust hyperpigmentation as our patient exhibited.

There are very few reports describing different patterns of capecitabine-induced hyperpigmentation in the literature. In the majority of these cases, hyperpigmentation was associated with the development of HFS and occurred in non-Caucasian patients.[1-8] Vickers et al reported on 3 non-Caucasian patients who developed hyperpigmentation of the palms and soles prior to severe HFS, and argued that hyperpigmentation may be a marker of HFS and impending toxicity.[4] Others have proposed that although the two entities may occur at the same time, they are separate syndromes with different mechanisms, though the mechanisms are still unclear.[1] One case reported on an African American patient with marked hyperpigmentation not only of the hands and feet, but of the face and oral mucosa as well, suggesting hyperpigmentation may occur independently of HFS.[1]

There are currently only five reported cases of capecitabine-induced hyperpigmentation in absence of HFS symptoms. One reported on a 41-year old African American woman receiving capecitabine for ovarian carcinoma.

Figure 1. New onset hyperpigmented macules below the eyes (arrows) and lateral aspects of the tongue (arrow heads).

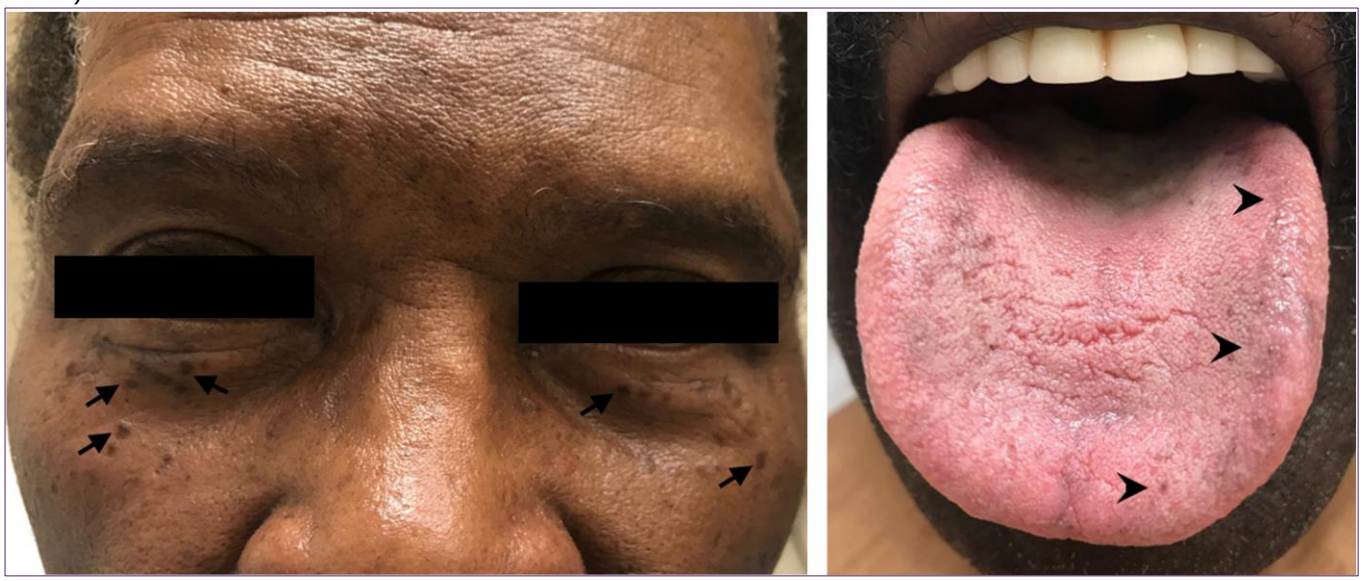
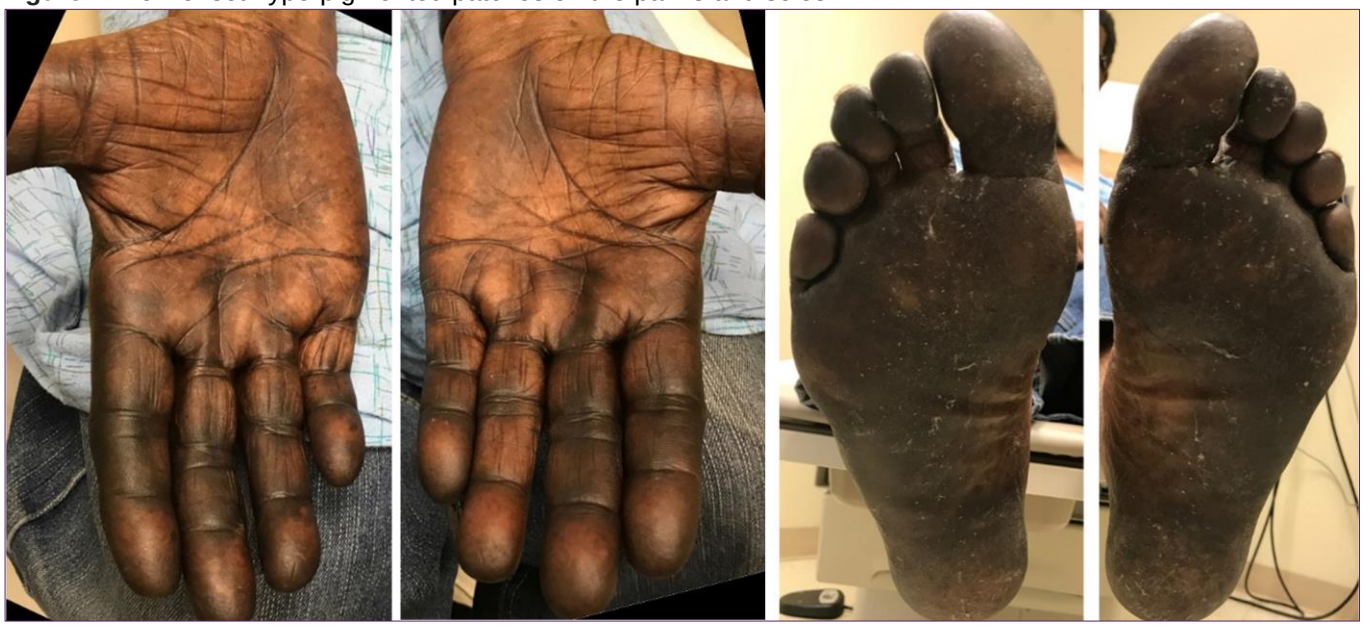


Figure 2. New onset hyperpigmented patches on the palms and soles.



This patient developed hyperpigmentation of the palmar creases and soles, and patchy hyperpigmentation of the tongue, which resolved 8-10 days after treatment.[5] In another case, a 59-year old Middle Eastern woman described similar findings of hyperpigmentation more apparent in the creases of her palms and soles, and well demarcated macules on the tongue.[9] She had complete resolution of the lesions at 10 weeks after discontinuation of capecitabine.

While the majority of capecitabine-induced hyperpigmentation reports involve patients with darker skin, the last three cases of hyperpigmentation in the absence of HFS include patients with fairer skin. In all three, hyperpigmentation presented as macules confined to the sole of the foot.[10,11] It is likely that this type of hyperpigmentation is common, yet underreported, especially in patients with darker skin types.

Overall, capecitabine is a well-tolerated and effective chemotherapeutic agent. This case, along with our prior experience, supports the idea that capecitabine-induced hyperpigmentation may occur as a distinct entity from HFS. There is no indication to alter dose or discontinue treatment upon the development of hyperpigmentation; however, it is important to advise patients to continue to monitor for changing symptoms indicative of HFS, such as edema, blistering, or desquamation. More research is required to help further understand the relationship between hyperpigmentation to capecitabine and other 5-FU derivatives and its underlying mechanism.

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