

# Serious Hand-and-Foot Syndrome in Black Patients Treated With Capecitabine: Report of 3 Cases and Review of the Literature

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*Hand-and-foot syndrome (HFS) is one of the well-known adverse events associated with capecitabine, a prodrug of 5-fluorouracil (5-FU). HFS, also known as erythrodysesthesia, manifests as acral erythema with swelling and dysesthesia of the palms and plantar aspects of the feet, and, in the absence of dosage reduction or stoppage of the drug, progresses to moist desquamation and ulceration with serious infections and loss of function. In black patients, we observed that capecitabine given in the recommended dosage leads to hyperpigmentation of the palms and soles, followed by a distinct keratoderma-like thickening not seen in white patients. Furthermore, in patients with a precarious peripheral vasculature, this condition evolves rapidly into grade 3 HFS, with ulceration and infection. We report our experience with capecitabine in 3 black patients and contrast it to that of 2 white patients. A brief review of the literature on fluoropyrimidines and HFS follows.*

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Recently, the US Food and Drug Administration approved capecitabine, an oral fluoropyrimidine, for the treatment of metastatic breast and colon cancers that fail to respond to standard chemotherapies.<sup>1</sup> The manufacturer lists hand-

and-foot syndrome (HFS) as one of the well-known adverse events that may be associated with this prodrug of 5-fluorouracil (5-FU).<sup>2</sup>

Capecitabine was designed to achieve sustained cytotoxic exposure of tumor cells without the inconvenience of intravenous (IV) administration of 5-FU and its associated systemic adverse toxic events. Specifically, we understand that the adverse events of capecitabine overlap with those of IV 5-FU, which are very familiar to oncologists. In our practice, for example, we observed that in black patients, the pattern of manifestations and the incidence of serious manifestations of HFS (grades 2 and 3) are different from those seen in white patients. We compare the cases of 3 black patients and 2 white patients who received capecitabine at similar dosages.

## Case Reports

**Patient 1**—A 58-year-old black man was seen one year after a surgery for colon carcinoma stage III (C2). He was started on a weekly regimen of adjuvant chemotherapy with 5-FU and leucovorin. The patient, who was diabetic, was receiving insulin injections twice a day. Before treatment was completed, the levels of carcinoembryonic antigen started to rise. Results of a computed tomography (CT) scan revealed a retroperitoneal mass. He was started immediately on a regimen of leucovorin, irinotecan, and 5-FU. In response to this regimen, he developed side effects of leukopenia and intermittent diarrhea, which were effectively managed. In addition, the patient developed mild scaly dermatitis with hyperpigmentation in his hands and left foot. The lower right leg had been amputated 3 years earlier because of diabetic peripheral vascular disease and gangrene. HFS was managed with

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**Figure 1.** Hyperpigmentation and hyperkeratosis of the dorsal aspects of the hands (A) and palms (B)(patient 1).

local applications of lubricants. The patient experienced minimal pain and discomfort when using his hands.

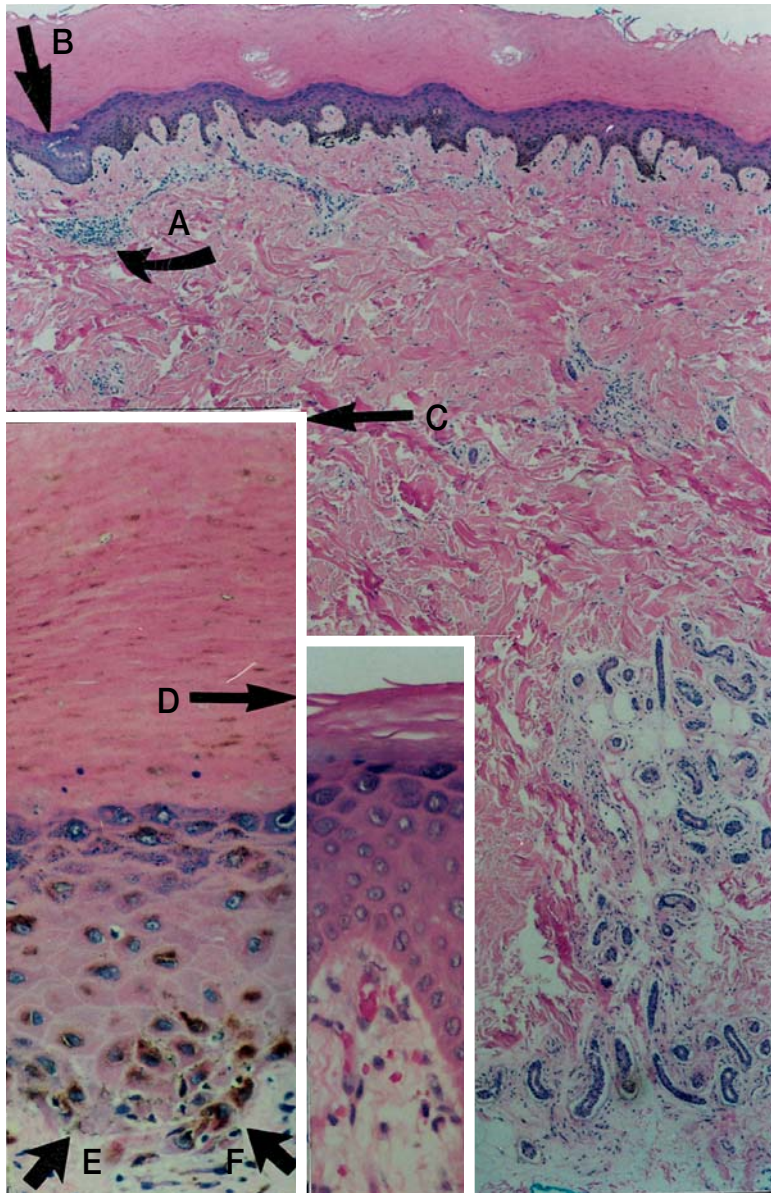
Four months before presentation, a CT scan revealed that the disease had progressed, with liver metastasis and elevated levels of carcinoembryonic antigen. After a discussion with the patient of potential side effects, capecitabine was prescribed as a third-line chemotherapeutic agent. The patient's renal functions were good, and he was given the usual dose of 2500 mg per square meter of body surface area twice daily (2 weeks on, 1 week off).

For 3 months, the patient tolerated the drug well with no systemic side effects. Slowly, however, he developed severe hyperpigmentation of the dorsal aspect of the palms and hands (Figure 1) and gradual thickening of the skin, leading to marked stiffness of the hands with pain and loss of function. This deteriorated rapidly into moist desquamation, with ulceration and infection in the left foot (Figure 2). Because the patient's lower right



**Figure 2.** Severe hyperpigmentation and hyperkeratosis of the left foot resembling impending gangrene (patient 1). The right foot is shown with an artificial-limb postamputation.





**Figure 3.** Compact hyperkeratosis with epidermal acanthosis and superficial perivascular lymphocytic infiltrate (A) and a normal opening of an eccrine gland duct (B). Coils of eccrine glands (shown in the lower right corner) with no significant changes (H&E, original magnification  $\times 40$ ) (patient 1). The large inset shows the epidermis (H&E, original magnification  $\times 400$ ). The small inset is taken at the same magnification from a biopsy of palmar skin with no epidermal pathology, and the difference in the thickness of the keratin layers of a normal palm (C and D) and keratoderma is apparent. The bottom of the large inset shows the vacuolar degeneration of the basal layer of the epidermis (E and F); nuclear pleomorphism and exocytosis of small lymphocytes also can be seen.

leg had been amputated after the development of gangrene, he needed hospitalization to prevent gangrene in his left foot. Radiography of the foot showed involvement of the underlying bone, and results of vascular studies revealed compromised circulation. He was scheduled for amputation of the lower left leg, as well.

A punch biopsy of the skin and subcutis from the right hand was performed, and results showed vacuolar degeneration of the basal layer of the epidermis with cellular enlargement, spongiosis, mild exocytosis of small lymphocytes, and marked hyperkeratosis (Figure 3). The dermis showed a mild superficial perivascular lymphocytic infiltrate.

The eccrine glands displayed no significant pathology. Relevant immunohistochemical findings included the demonstration that Langerhans cells were markedly decreased and that all lymphocytic reactions were of T-cell origin.

*Patient 2*—A 78-year-old nondiabetic black man presented with abdominal pains and signs of intestinal obstruction. A CT scan revealed a mass in the ascending colon, with small bowel obstruction and liver metastasis. He underwent palliative bypass surgery. A biopsy of the liver was performed, and results revealed metastatic colon carcinoma. He was treated initially with leucovorin, irinotecan (CPT-11), and 5-FU, but after



**Figure 4.** Palms of the hands show hyperkeratosis and hyperpigmentation. The condition improved with reduction of the dose of capecitabine (patient 2).



**Figure 5.** Palms of the hands with only palmar erythema after 6 months of treatment with full doses of capecitabine (patient 4).

4 months of treatment, the disease progressed and led to severe diarrhea.

The patient was started on capecitabine (2500 mg per square meter of body surface area) in divided doses. Initially the patient tolerated it well; however, he slowly developed disabling, progressive keratodermalike changes, with swelling and thickening of the skin of the palms (Figure 4) and soles and hyperpigmentation. The drug was discontinued for 2 weeks and afterward resumed with 1000-mg doses twice daily (2 weeks on, 1 week off), resulting in marked improvement of the pain and stiffness. However, the disease progressed, and the patient was placed under hospice care.

*Patient 3*—A 38-year-old black woman was first seen for weight loss; lower abdominal pain; and the presence of a hard nodular mass in her lower abdomen, which, based on sonographic findings, was thought to be an ovarian mass. Carcinoembryonic antigen levels were greater than 100 U/mL, and serum levels of CA 125 were within the reference range. Subsequently, surgery identified a large sigmoid colon carcinoma that was fixed to the pelvis with mesenteric metastatic lesions. The liver was free of disease. A palliative colostomy was performed, and results of a biopsy of the lesions confirmed the diagnosis of colonic adenocarcinoma.

The patient received weekly infusions of leucovorin, irinotecan, and 5-FU (3 weeks on, 1 week off). She had tolerable symptoms of diarrhea and mucositis and minimal complaints about her hands and feet. The disease progressed for about 4 months, with involvement of the liver associated with profound weight loss and anorexia. The patient was

started on capecitabine. After a 2-cycle regimen, she developed pain, stiffness, and keratodermalike thickening of the skin of the palms and soles, with marked hyperpigmentation. She experienced a painful Raynaud phenomenon during the winter and was unable to use the computer keyboard at work. She also developed noticeable hyperpigmentation of the entire body. The dosage of the drug was reduced. Rapid progression of the disease resulted in liver failure, ascites, and death.

*Patient 4*—A 78-year-old white man was given leucovorin, irinotecan, and 5-FU for metastatic colon cancer to the liver for about 6 months. Because of disease progression, he was started on capecitabine (2500 mg per square meter of body surface area). With this chemotherapy, the disease stabilized for more than 6 months. During this time, he developed only mild erythema of the hands and soles (Figure 5). Eventually, some disease progression occurred with the appearance of pulmonary nodules at the base of his right lung, as well as evidence of hepatic failure.

*Patient 5*—A 72-year-old white woman with a history of right modified radical mastectomy followed by chemotherapy presented with a recurrence of lobular carcinoma in the chest wall. She was given both oral capecitabine (2500 mg per square meter of body surface area) and infusions of vinorelbine every 3 weeks. After 3 months, no signs of HFS were seen.

### Comment

In 1974, Zuehlke<sup>3</sup> reported erythematous eruption of the palms and soles associated with mitotane

therapy. Subsequently, the literature referred to this condition as acral erythema, palmar-plantar erythrodysesthesia syndrome, and, most recently, as HFS. HFS has been observed as an adverse event in many chemotherapeutic agents and regimens; however, cytarabine, doxorubicin, and fluorouracil are the agents most commonly cited.<sup>4</sup>

The severity of the manifestations of HFS is classified into 3 grades.<sup>2</sup> Grade 1 consists of erythema of the lateral aspects of the fingers that progress to the thenar and hypothenar eminences, with swelling, numbness, dysesthesia/paresthesia, and tingling, especially over the pads of the distal phalanges. The same manifestations occur on the soles and less frequently on the dorsal aspects of the hands and feet. Grade 2 is a progression of grade-1 manifestations, where pain and discomfort affect the daily activities of the patient. Grade 3 is the superimposition of blistering, moist desquamation and ulceration, and severe pain.

The manufacturer of capecitabine lists HFS first in the adverse reactions section of the drug's product information.<sup>2</sup> Cessation of the medication is recommended by the manufacturer for HFS grades 2 and 3 until the event resolves or decreases in intensity. In 1999, results of a large phase III study comparing oral capecitabine with IV fluorouracil plus leucovorin in patients with colorectal cancer were published.<sup>5</sup> This study showed that HFS was the most frequently reported adverse reaction (all grades) in the capecitabine group, affecting approximately 50% of patients; furthermore, grade-3 HFS was reported in 16.2% of patients in the capecitabine group compared with 0.3% in the 5-FU/leucovorin group.

Recognition and identification of the signs and symptoms of grade-1 HFS in patients receiving capecitabine are important to avoid progression to grade 2 or to the more debilitating grade 3. Available data on this subject do not segregate patients according to race.<sup>5,6</sup> In our practice, we observed that black patients treated with capecitabine develop HFS more frequently than white patients. Most important, however, their manifestations of HFS are different from those described in the literature.

First, the classic signs and symptoms of grade-1 HFS are camouflaged in black patients; instead, they develop a progressive hyperpigmentation of their palms and soles, and, in one patient, the entire body. Second, there is a concomitant gradual thickening of the skin of the palms and soles that leads to stiffness of the hands and feet, with pain and loss of function. Third, black patients with diabetes may deteriorate rapidly into a severe

form of grade-3 HFS, leading to life-threatening complications and the possibility of amputation. A precarious peripheral circulation may precipitate grade-3 HFS as seen in patient 1, who had a history of diabetes mellitus and peripheral vascular disease. Our black patients had mild manifestations of the usual HFS when they were given IV 5-FU.

One case of palmar-plantar keratoderma secondary to tegafur, another oral fluoropyrimidine, was reported in the literature.<sup>7</sup> A 31-year-old woman of unspecified race developed diffuse thickening of the palms and soles 10 months after starting tegafur as adjuvant therapy for sigmoid colon adenocarcinoma. She complained of severe pain in her feet and hands that interfered with walking and hand grasping. Tegafur therapy was discontinued, and the keratoderma subsided slowly within the subsequent 5 months; however, the dysesthesia persisted for 2 more months. The term *keratoderma* was coined for this chronic acral erythema that evolved over a 10-month period.

We feel that the definition of grade-1 HFS for black patients should be revised to include hyperpigmentation of the palms and soles instead of erythema, and that progression to grade-2 HFS should consist of palmar-plantar keratoderma. The latter may take place within a relatively short period of 3 months. Transition from grade 2 to grade 3 may be abrupt and life threatening, especially in patients with preexisting peripheral vascular disease.

The pathologic changes of the skin biopsy taken from the hand of our first patient were studied. There was evidence of subacute damage to the basal layer of the epidermis manifested as vacuolar degeneration and abnormal maturation of the keratinocytes with nuclear pleomorphism and cytoplasmic enlargement, resulting in compact hyperkeratosis where the keratin layer is several times thicker than the normal basket-weave pattern seen in orthokeratosis. The only appreciable dermal pathologic change was a sparse, superficial T-cell lymphocytic infiltrate. A loss of Langerhans cells in the epidermis occurred, which could be attributed to the hostile environment created by the altered keratinocytes. We did not observe any of the changes of the eccrine glands reported as eccrine squamous syringometaplasia by Rongioletti et al<sup>8</sup> and Valks et al.<sup>9</sup>

The pathophysiology of HFS is unknown. However, the selective involvement of the epidermis of the palms and soles, accompanied sometimes by damage to the epithelial cells of the eccrine ducts, suggests that there is more to this syndrome than plain, direct toxic effect to the basal keratinocytes. The drug may be unraveling certain antigenic



determinants specific to the keratinocytes of the palms and soles, and the role of the immune system in the chain of events that lead to palmar-plantar keratoderma cannot be discounted.

### Conclusion

Our experience with oral capecitabine shows that HFS is a serious adverse event that has to be taken into account whenever capecitabine is contemplated in a patient with peripheral vascular disease. Also, we learned that in the black patients we treated, the syndrome starts with acral hyperpigmentation rather than by erythema, and that disabling palmar-plantar keratoderma develops rather quickly (within 3–6 months) in black patients and is rarely seen in white patients. Finally, more research is needed to look at the true incidence of HFS among the different races.

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