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"Navigating through a case of Capecitabine-Induced Hand-Foot Syndrome"

B Sai Rithika Reddy (1), Sukesh Gautam S(2)

1. Post graduate student, Department of Dermatology, Venereology and Leprosy, Saveetha Medical College and Hospital, Chennai, India
2. Assistant Professor, Department of Dermatology, Venereology and Leprosy, Saveetha Medical College and Hospital, Chennai, India

Corresponding Author- B Sai Rithika Reddy, rithikareddy033@gmail.com

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Abstract

Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is widely used for treating colorectal and breast cancers. One of its dose-limiting toxicities is Hand-Foot Syndrome (HFS), a dermatological adverse effect characterized by hyperpigmentation, erythema, and sensory disturbances of the palms and soles. Here, we present a case of Grade 1 HFS in a 48-year-old male with rectosigmoid adenocarcinoma (T3 N0 M0) following a Hartmann procedure. The patient was started on capecitabine 500 mg three times daily as part of adjuvant chemotherapy. Fifteen days after therapy initiation, the patient developed bilateral black discoloration of the palms and soles accompanied by mild sensory loss but no blistering, swelling, or ulceration. Physical examination confirmed Grade 1 HFS. A skin biopsy revealed chronic nonspecific dermatitis, and routine blood investigations were within normal limits. The diagnosis of capecitabine-induced HFS was established based on the temporal relationship to therapy and exclusion of other causes. The capecitabine dose was reduced, and supportive care with emollients, topical corticosteroids (betamethasone), and multivitamins was initiated. Over four weeks, the patient's symptoms improved significantly, allowing continuation of therapy without further complications. This case highlights the importance of early recognition and intervention in managing HFS to prevent symptom progression and ensure treatment adherence, thereby optimizing oncological outcomes.

Introduction

Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is a widely used chemotherapeutic agent for colorectal and breast cancers due to its convenience and efficacy [1]. One of the most significant dose-limiting toxicities associated with capecitabine is Hand-Foot Syndrome (HFS), also known as palmar-plantar erythrodysesthesia. HFS is characterized by erythema, hyperpigmentation, swelling, and desquamation of the palms and soles, often accompanied by pain, numbness, or functional impairment [2]. The incidence of HFS can vary depending on the dose and duration of capecitabine therapy, with higher cumulative doses increasing the risk [3].

The pathophysiology of HFS remains incompletely understood but is thought to involve the accumulation of active metabolites of capecitabine in the eccrine sweat glands of the palms and soles. This localized exposure induces inflammatory responses, leading to characteristic clinical manifestations such as hyperpigmentation, dysesthesia, and in severe cases, ulceration [4,5]. The National Cancer Institute (NCI) classifies HFS into three grades based on symptom severity, with Grade 1 being the mildest form, often presenting as painless erythema and pigmentation changes [6].

The development of hyperpigmentation in HFS, as observed in this case, is particularly common and has been reported as a side effect of capecitabine in several studies [7]. Management typically involves supportive measures such as emollients, topical corticosteroids, dose reduction, and multivitamin supplementation [8]. Early recognition and intervention are crucial to ensure adherence to therapy without compromising the patient's quality of life.

This case highlights Grade 1 HFS in a 48-year-old patient with rectosigmoid adenocarcinoma receiving

capecitabine therapy following a Hartmann procedure. Prompt dose adjustment and supportive treatment led to significant improvement in symptoms.

Case Details

A 48-year-old male presented with complaints of black discoloration of the palms and soles and a mild loss of sensation, occurring approximately 15 days after initiating capecitabine therapy. The patient was diagnosed with rectosigmoid adenocarcinoma (T3 N0 M0) and had undergone Hartmann procedure. Post-operatively, the patient was started on capecitabine 500 mg three times daily, as part of adjuvant chemotherapy.

Clinical Presentation: The patient reported progressive darkening of the palms and soles, which he noticed about two weeks into treatment. The hyperpigmentation was diffuse, covering the palmar and plantar surfaces, without accompanying blistering, or ulceration. He described a mild tingling sensation and discomfort in the affected areas, but there were no functional limitations. The discoloration caused significant concern, prompting clinical evaluation. On physical examination, there was prominent bilateral hyperpigmentation of the palms and soles consistent with Grade 1 Hand-Foot Syndrome (HFS), as per the National Cancer Institute (NCI) grading criteria. There was no associated swelling, fissuring, or ulceration, and the discoloration was asymptomatic apart from mild sensory alterations. No systemic symptoms such as fever, malaise, or gastrointestinal disturbances were reported.

To exclude other potential causes of hyperpigmentation, further investigations were performed.

Skin Biopsy: A biopsy from the affected area showed chronic nonspecific dermatitis with no evidence of vasculitis or other dermatoses. Routine Blood Workup: Complete blood count (CBC): Normal, Liver function tests (LFTs) and renal profile: Within normal limits, Serum electrolytes: Normal.

Capecitabine Adherence: Medication history confirmed regular adherence to prescribed chemotherapy. Given the temporal association with capecitabine initiation and the absence of systemic abnormalities, a diagnosis of capecitabine-induced Hand-Foot Syndrome (Grade 1) was established.

Capecitabine dose was reduced in line with established protocols for chemotherapy-induced HFS. The patient was advised supportive care measures, which included:

Topical emollients: Intensive moisturizing to soothe the affected areas**.** Topical steroids: Betamethasone dipropionate ointment was prescribed to reduce inflammation and discomfort. Multivitamins: Supplementation with pyridoxine (Vitamin B6) and general multivitamins was initiated, although evidence regarding pyridoxine efficacy remains inconclusive [1]. Patient education: The patient was advised to avoid exposure to heat, pressure on the palms and soles, and activities that may exacerbate symptoms.

During follow-up visits over the next 4 weeks, the patient showed gradual improvement. The hyperpigmentation on the palms and soles lightened significantly, and the tingling sensation resolved completely. Importantly, no new lesions developed. The patient was able to continue chemotherapy with dose adjustments, and his functional status remained unaffected.

Discussion

Hand-Foot Syndrome (HFS), also referred to as palmar-plantar erythrodysesthesia, is a well-recognized adverse event associated with chemotherapeutic agents such as capecitabine, 5-fluorouracil (5-FU), and liposomal doxorubicin. The pathophysiology of HFS is multifactorial, with the accumulation of active metabolites of capecitabine (5-FU) in the skin of the palms and soles being a key contributing factor. These regions are predisposed due to high concentrations of eccrine sweat glands, leading to localized toxic effects when the metabolites are excreted through sweat during therapy [7]. This case highlights Grade 1 HFS, presenting as bilateral palmar and plantar hyperpigmentation, a relatively mild but distressing presentation for the patient. The clinical manifestations of HFS range from erythema, numbness, and tingling in early stages (Grade 1), to painful swelling, desquamation, and ulceration in severe cases (Grades 2 and 3, respectively) [2]. In this patient, diffuse hyperpigmentation and mild sensory loss were the predominant features, with no evidence of blistering, fissuring, or functional limitations, indicating Grade 1 toxicity as per the National Cancer Institute (NCI) criteria.

In this case, the patient developed **black discoloration** of the palms and soles without blistering, swelling, or functional impairment, consistent with Grade 1 HFS. A similar case reported by **Nguyen et al.** documented diffuse palmar and plantar pigmentation in a 52-year-old patient receiving capecitabine for metastatic breast cancer [10]. The hyperpigmentation resolved after dose reduction and topical emollients, reinforcing the role

of early intervention. Another report by **Wang et al.** described a patient on capecitabine presenting with pigmentation not only on palms and soles but also over nails, suggesting a spectrum of capecitabine-associated skin toxicities [11]. While hyperpigmentation remains a common early sign of capecitabine toxicity, the degree and distribution may vary. Unlike cases involving nail pigmentation or systemic involvement, this case presented with localized **palmar-plantar changes**, simplifying diagnosis and management.

The hyperpigmentation in the present case appeared **15 days after therapy initiation**, aligning with findings from other case studies: A case by **Nagore et al.** reported HFS developing within **2 to 4 weeks** of starting capecitabine therapy in colorectal cancer patients [3]. This timeframe reflects the cumulative nature of the toxicity and highlights the importance of monitoring patients closely within the first few weeks of treatment. In contrast, **Saif et al.** reported cases of delayed HFS, occurring after 6-8 weeks of treatment, suggesting that cumulative dosage plays a critical role [7]. The current case demonstrated **early-onset HFS**, underscoring the importance of clinician vigilance during the initial phase of capecitabine administration.

Skin hyperpigmentation is a common but underreported side effect of capecitabine therapy. Several reports have noted pigmentation changes on palms, soles, and occasionally the nails, which can cause significant cosmetic concerns [3]. In this case, a skin biopsy confirmed chronic nonspecific dermatitis, ruling out other potential causes of pigmentation such as nutritional deficiencies, Addison's disease, or other dermatoses. This finding underscores the importance of correlating clinical presentation with histopathology to establish an accurate diagnosis. Histopathology in this case revealed **chronic nonspecific dermatitis**, a common finding in capecitabine-induced HFS. Similar findings were reported in a case by **O'Reilly et al.**, where biopsy showed **nonspecific inflammation** with no evidence of vasculitis or infections [8]. However, some case reports have described more prominent changes, including **hyperkeratosis** and **epidermal thinning**, particularly in patients with severe Grade 2 or Grade 3 HFS [12]. In this case, the mild **nonspecific dermatitis** correlates with the clinical grade of toxicity (Grade 1), whereas more severe histological changes tend to appear with higher grades of HFS.

The cornerstone of managing HFS involves early recognition, dose modification, and supportive care. Current guidelines recommend the following approaches for Grade 1 HFS: Topical emollients to restore skin barrier integrity and provide symptomatic relief [4]. Topical corticosteroids, such as betamethasone, to reduce inflammation. Vitamin supplementation: Pyridoxine (Vitamin B6) is often used empirically; however, evidence supporting its efficacy remains controversial. A randomized controlled trial by Kang et al. found no significant benefit of pyridoxine in preventing HFS [5]. Capecitabine dose reduction or temporary interruption may be necessary to prevent progression to severe HFS while maintaining therapeutic efficacy.

In this case, a combination of topical emollients, steroids, multivitamin supplementation, and dose reduction led to significant improvement. The patient's symptoms resolved over 4 weeks, and chemotherapy could be continued without further interruptions. The current case was managed with **capecitabine dose reduction, emollients, topical corticosteroids**, and multivitamins, resulting in significant improvement over 4 weeks. Similar management strategies have been highlighted in other case reports. For instance, **Saif et al.** described the successful use of **topical emollients and corticosteroids** in alleviating symptoms of HFS [7]. **Kang et al.** reported that pyridoxine (Vitamin B6), often used in such cases, did not provide significant clinical benefit in preventing or reducing HFS [5]. This case highlights the effectiveness of supportive care combined with **dose adjustment** in managing mild HFS, a consistent finding across multiple case reports. Early intervention prevented progression to higher grades and ensured continuation of therapy.

Dose reduction of capecitabine is often necessary in cases of HFS to prevent worsening of symptoms while maintaining treatment efficacy. A review by **Twelves et al.** demonstrated that **dose modification** in response to toxicity does not compromise the efficacy of capecitabine-based regimens for colorectal cancer [9]. In contrast, failure to recognize early symptoms can lead to severe HFS, causing **treatment interruptions** and negatively impacting therapeutic outcomes, as seen in reports by **Webster-Gandy et al.** [4]. In this case, timely dose reduction allowed symptom resolution without treatment cessation, underscoring the importance of proactive toxicity management to optimize patient outcomes.

While Grade 1 HFS is often considered mild, its impact on patient quality of life and adherence to chemotherapy cannot be underestimated. The discomfort and cosmetic changes, such as hyperpigmentation,

may cause psychological distress and reduce compliance with therapy. Studies have shown that dose delays or reductions due to HFS occur in up to 50% of patients receiving capecitabine-based regimens [9]. Early intervention, as demonstrated in this case, can prevent symptom progression and allow for continuation of treatment, ensuring optimal oncological outcomes. This case emphasizes the importance of awareness and timely management of HFS among oncologists and dermatologists. Early identification of symptoms, coupled with appropriate interventions, can mitigate toxicity and improve treatment tolerability. Moreover, patient education regarding self-care measures, such as avoiding excessive pressure, heat, and irritants to the palms and soles, is crucial in preventing exacerbations of HFS. Capecitabine-induced HFS is a dose-dependent dermatological toxicity that requires prompt recognition and management. This case illustrates a relatively mild presentation of HFS with bilateral palmar and plantar hyperpigmentation, which resolved with supportive care and dose adjustment. Clinicians must maintain a high index of suspicion for HFS in patients on capecitabine therapy and employ multidisciplinary approaches to ensure optimal patient outcomes.

Conclusion

Capecitabine-induced Hand-Foot Syndrome (HFS) is a common but manageable dermatological toxicity seen in patients undergoing chemotherapy for various malignancies, including colorectal cancer. This case highlights the early onset of Grade 1 HFS, presenting as bilateral palmar and plantar hyperpigmentation with mild sensory loss, occurring 15 days after therapy initiation. The prompt recognition of symptoms and timely intervention through capecitabine dose reduction, supportive measures such as emollients and topical corticosteroids, and patient education were critical in preventing symptom progression. Comparisons with similar case reports reinforce that early identification of HFS and its appropriate management can allow patients to continue chemotherapy effectively without compromising outcomes. Clinicians must remain vigilant for early signs of HFS, particularly during the initial phases of capecitabine therapy, as this toxicity can significantly impact a patient's quality of life and treatment adherence. Multidisciplinary approaches, including dermatological support and patient education, play a pivotal role in achieving optimal therapeutic outcomes. Further studies are warranted to explore additional preventive strategies and improve management protocols for capecitabine-induced HFS, ensuring a balance between therapeutic efficacy and treatment tolerability.

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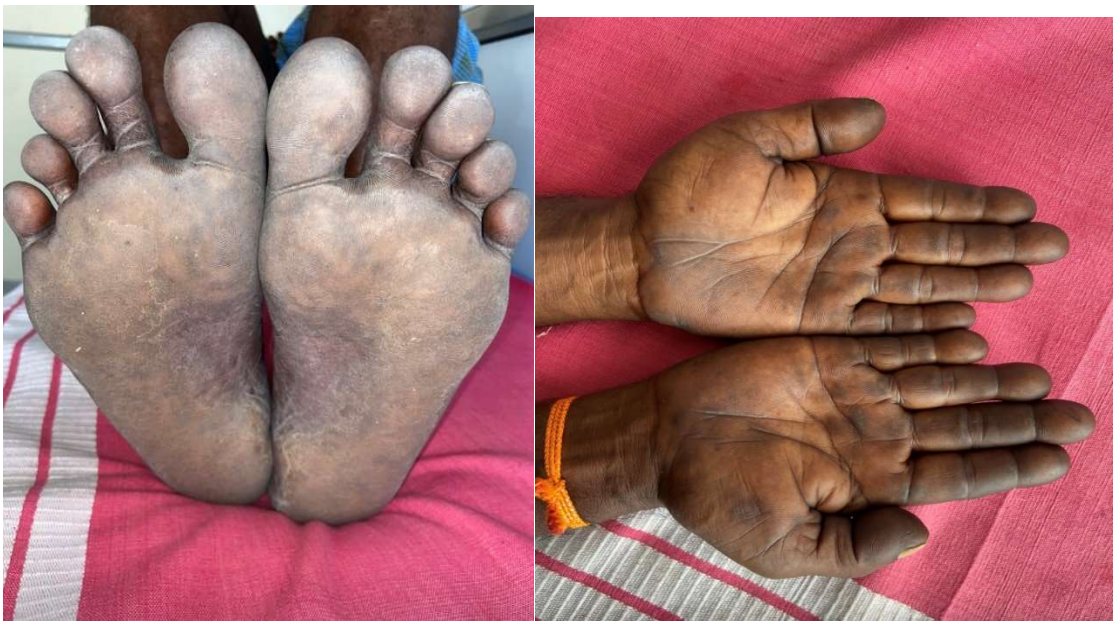

1. Grade 1 HFS noted over bilateral palms and soles after Capecitabine therapy

2. Clinically significant improvement noted in pigmentation after 4 weeks of management