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Case Report

Squamous Cell Cancer of the Skin in a Patient on Maintenance Capecitabine for Metastatic Breast Cancer: A Case Report

Sidharth Mahajan[1]*, Heather Moore[2], Puneet Jolly[3], Gretchen Kimmick[2]

[1]Department of Internal Medicine, MacNeal Hospital, Berwyn, Illinois, USA
[2]Department of Breast Cancer, Duke Cancer Center, Durham, North Carolina, USA
[3]Department of Dermatology, University of North Carolina, Chapel Hill, North Carolina, USA

Abstract

Capecitabine is a widely used and effective oral chemotherapeutic agent for metastatic breast cancer and colorectal cancer; however, it is associated with several adverse effects. Of these effects, hand–foot syndrome (HFS) or palmar–plantar erythrodysesthesia, characterized by chronic inflammation, particularly of the hands and feet, is most notable. Chronic inflammation increases the risk of squamous cell cancers. We present a unique case of a patient with metastatic breast cancer whose disease was controlled with capecitabine for over a decade. She experienced chronic grade 1–2 HFS and subsequently developed squamous cell skin cancer on the palms and soles. To the best of our knowledge, squamous cell cancer associated with capecitabine exposure has not been previously reported. This case report aims to shed light on this association, thereby expanding the existing literature on the topic.

Keywords: Breast cancer, capecitabine, hand–foot syndrome, palmar–plantar erythrodysesthesia, squamous cell cancer

Introduction

Capecitabine (Xeloda) is an oral prodrug of 5-fluorouracil used to treat breast and colorectal cancers.[1] It is metabolized to 5-fluorouracil predominantly in tumor cells, thereby minimizing the systemic side effects. However, the abundant expression of thymidine phosphorylase in the hands and feet leads to inflammation, termed hand–foot syndrome (HFS) or palmar–plantar erythrodysesthesia.[1,2] Risk factors for squamous cell cancer (SCCa) of the skin include ultraviolet (UV) exposure, tobacco use, and chronic inflammation, while tobacco and alcohol use, human papillomavirus (HPV) infection, betel nut chewing, radiation exposure, and other environmental and occupational exposures are risk factors for SCCa of the head and neck.[3,4] We present a rare case of SCCa in a patient whose metastatic breast cancer was controlled for 10 years with capecitabine.

Case Report

A 48-year-old premenopausal woman presented with hormone receptor-positive, human epidermal growth factor receptor

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Address for correspondence: Dr. Sidharth Mahajan, Department of Internal Medicine, MacNeal Hospital, Berwyn, Illinois, USA.
E-mail: sidharthmahajan321@gmail.com

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2-negative, locally advanced left breast cancer with metastases to the liver and lungs. She had a 25-pack-year history of tobacco use, having quit 5 years before the diagnosis but no history of alcohol or betel nut use. There was no relevant family medical history. She was initially treated with medical ovarian suppression (goserelin) and endocrine therapy; however, the disease rapidly progressed. Consequently, her treatment protocol was altered to include docetaxel and capecitabine.

Docetaxel was administered at a dosage of 75 mg/m^2 once every 3 weeks, along with capecitabine 1000 mg/m^2 twice daily, eventually escalated to 1500 mg twice daily, given on days 1–14 of a 21-day cycle. However, after four cycles of treatment, she developed grade 1 HFS, necessitating adjustments to both medications with capecitabine back to 1000 mg/m^2 twice daily. To alleviate symptoms, she applied various topical emollients including bag balm, Blue-Emu cream, and other thick emollient creams. Remarkably, she achieved a complete clinical response after 1 year of this treatment; subsequently, docetaxel was discontinued and she continued to receive single-agent capecitabine.

Capecitabine was continued for 11 years, during which the clinical course was remarkable for:

1. Surgeries and radiation to manage ipsilateral right breast cancer and the progression of the cancer in the left breast
2. Diagnosis of a variant of undetermined significance in BRCA2, and no other mutations detected
3. Ongoing management of chronic, grade 1–2 HFS.

The management of HFS also included participation in a clinical trial of sildenafil. During therapy, she underwent treatment for actinic keratoses, with three lesions on her nose treated with cryotherapy and surgical excision. She continued to experience skin issues despite discontinuing capecitabine, including HFS and verruca vulgaris on her left mid-palm and left digits, for which she was treated with salicylic acid and Aldara cream. Three years postdiscontinuation, she presented with a nonhealing, ulcerated wound on her right foot as shown in Figures 1 and 2, diagnosed as well-differentiated SCCa on biopsy after excision via Mohs surgery.

After over a decade of treatment with capecitabine, she presented with pain in her left inner cheek, accompanied by a whitish plaque and no evidence of oral ulcers. She was treated with antiviral agents for a suspected oral herpetic lesion, topical steroids for presumed lichen planus, and surgery for presumed salivary gland stones, with no relief. After 2 years of recurrent symptoms, she was diagnosed with non-HPV-related SCCa of the buccal mucosa.

Discussion

HFS is a common side effect in patients undergoing chemotherapy with agents such as docetaxel, 5-fluorouracil, and capecitabine (Xeloda).[5] Initially, it manifests as palmoplantar paresthesia, erythema, extreme dryness, and itching in the palms and soles, progressing to cracking, ulceration, and blister formation with prolonged drug exposure.[6,7]

Capecitabine, a prodrug metabolized into 5-fluorouracil, is activated by thymidine phosphorylase, which is more abundant in the palms and soles. Consequently, the accumulation of metabolites in these areas indirectly activates the cyclooxygenase-2 (COX-2) enzyme, leading to chronic inflammation and edema.[8] Chronic irritation is among the well-recognized predisposing factors leading to the development of SCCa. Chronic irritation, UV exposure, and tobacco use (as in our patient who had a significant history of tobacco use) stimulate the upregulation of COX-2 expression, leading to increased prostaglandin (PGE2) production and the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 (IL-1), and IL-6, causing a state of chronic inflammation associated with cancer development.[9,10]

Preventive measures for SCCa include UV protection, smoking cessation, and regular monitoring of high-risk patients.[11-13] Reducing HFS associated with capecitabine

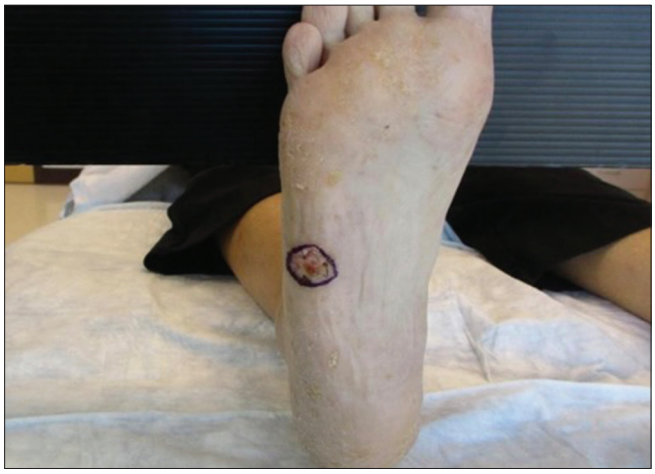

Figure 1: Ulcerated wound on the lateral plantar surface of the right foot

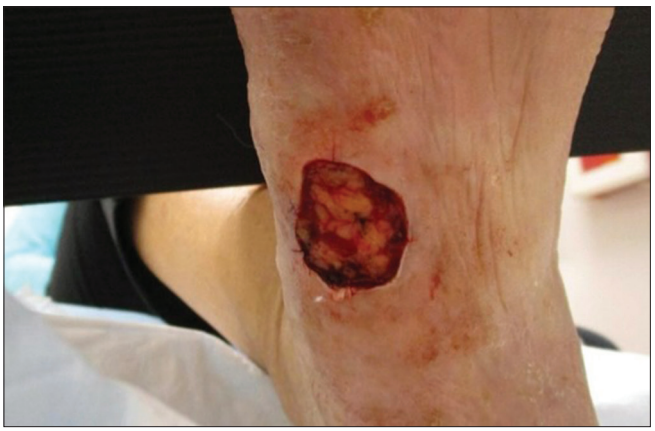

Figure 2: Progression of the wound on the lateral plantar surface of the right foot

may also be important in preventing long-term complications. The application of a topical anti-inflammatory has been shown to reduce HFS. The diclofenac-topical for reduction of capecitabine-related HFS trial (abstract 12,005) showed that topical diclofenac significantly reduced the incidence of grade 2 or higher HFS compared to placebo (3.8% vs. 15.0%, $P = 0.003$) in patients on capecitabine, with lower all-grade HFS rates (6.1% vs. 18.1%) and fewer capecitabine dose reductions due to HFS (3.8% vs. 13.5%) compared to those receiving placebo.[14] Alternative dose schedules may also reduce HFS. The X-7/7 study demonstrated that a fixed-dose regimen of capecitabine (1500 mg twice daily on a 7-day on, 7-day off schedule) led to fewer treatment discontinuations, dose modifications, and grade 3 or higher toxicities compared to the standard Food and Drug Administration-recommended dosing.[15]

Recent literature highlights the protective effects of low-dose oral capecitabine in treating and preventing nonmelanoma skin cancer in solid-organ transplant patients at 0.5–1.5 g/m^2 daily for 14 days in a 21-day cycle.[16] However, this dosage also resulted in side effects in up to 30% of the patients, including HFS as in our patient. Further research is needed to understand the mechanism of capecitabine and the optimal dosage to minimize side effects such as HFS.

Conclusion

In summary, this case establishes a potential association between chronic capecitabine therapy and the development of SCCa. The unusually long duration of therapy in this patient is likely to have played a role in this complication; however, to the best of our knowledge, an association between SCCa and past capecitabine use has never been studied or reported. Given the increasing use of capecitabine and also reports on its protective effect on nonmelanoma skin cancer, further investigations into the frequency of SCCa in patients exposed to capecitabine are needed. In the meantime, skin cancer screening, including careful attention to the hands and feet, is indicated.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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