Capecitabine-induced Systemic Lupus Erythematosus and Palmoplantar Erythrodysesthesia

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ABSTRACT

Capecitabine is emerging as an important drug in the treatment of metastatic breast and colorectal cancers. Marketed as Xeloda®, this prodrug is taken orally and readily absorbed. It is novel in its increased convenience for patients, similar efficacy to the intravenous form of its active metabolite and its increased tolerability.[1] We present a woman with metastatic breast cancer who presented with cutaneous abnormalities two months after starting treatment with capecitabine. Various dermatologic side effects have been attributed to capecitabine, often requiring cessation of the offending drug. We describe an unreported dermatological side effect of capecitabine therapy, systemic lupus erythematosus concurrent with palmoplantar erythrodysesthesia. As the use of this chemotherapeutic agent becomes more prevalent, it is important to recognize the range of its cutaneous side effects.

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INTRODUCTION

A 54-year-old woman with a history of metastatic breast carcinoma with bilateral mastectomy presented for evaluation of a new-onset rash after initiation of treatment with capecitabine. The patient has a past medical history significant for a naproxen allergy, which causes anaphylaxis, osteoarthritis of the left hip treated with total hip arthroplasty in 2007, and a 35 pack-per-year smoking history. The patient denied a personal or family history of "lupus."

In 2007, she noticed a mass in her right breast and was soon diagnosed with invasive ductal carcinoma of the right breast and lobular carcimona in situ of the left breast. At this time, she was treated with modified radical mastectomy of the right breast with axillary lymph node dissection and left simple mastectomy. The lymph nodes were positive for metastasis, and she began treatment with doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) in March of 2008. After four cycles, she completed an additional course of docetaxel ending in November 2008. A month later, the patient noted a swelling in her neck; a left supraclavicular lymph node biopsy in early 2009 showed metastatic carcinoma consistent with spread of her primary breast tumor.

In March of 2009, she began treatment with capecitabine at 3,500 mg daily and developed an erythematous rash on her face and chest around the fourth day. She denied any itching, pain, or numbness. She stopped taking capecitabine on the eleventh day of treatment and the rash began to subside, and following treatment with doxycycline 100 mg daily, the rash improved significantly. The patient then started the second cycle of capecitabine at a 25% dose reduction along with another course of doxycycline.

The eruption waxed and waned, with exacerbations occurring during courses of chemotherapy and modest improvement between treatments. There was no improvement in the dermatitis following the decreased dose. After the second round of chemotherapy with capecitabine, the patient developed painful blistering of her hands and feet consistent with palmoplantar erythrodysesthesia (PPE) (Figure 1). During the third round of chemotherapy at the same dose, she experienced worsening PPE, which prevented her from ambulating. With the emergence of this intolerable side effect, the oncologist stopped the drug mid-treatment and switched her chemotherapy to IV ixabepilone. The patient experienced complete resolution of the PPE two months after cessation of capecitabine, with the facial eruption improved but not completely resolved.

FIGURE 1. Changes compatible with palmoplantar erythrodysesthesia on the left hand

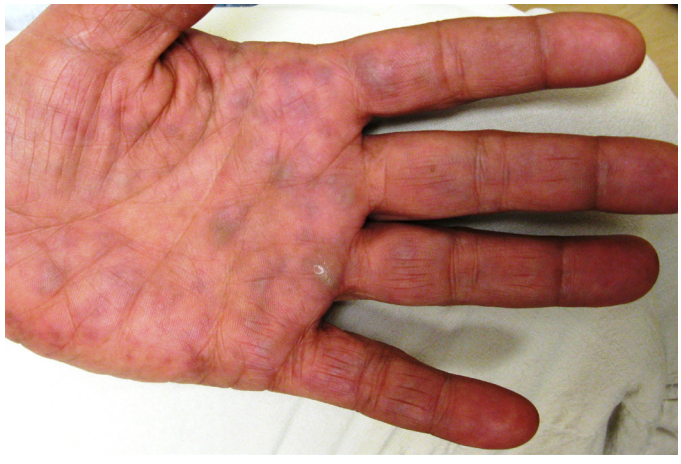
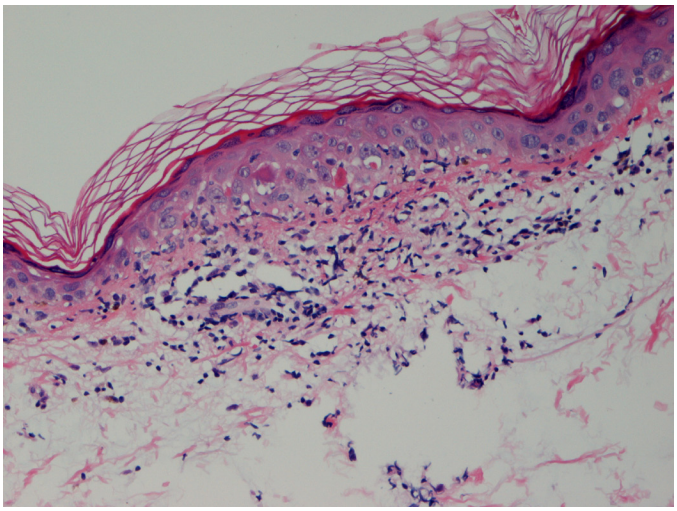


FIGURE 3. Biopsy from left arm with hyperkeratosis and focal interface dermatitis



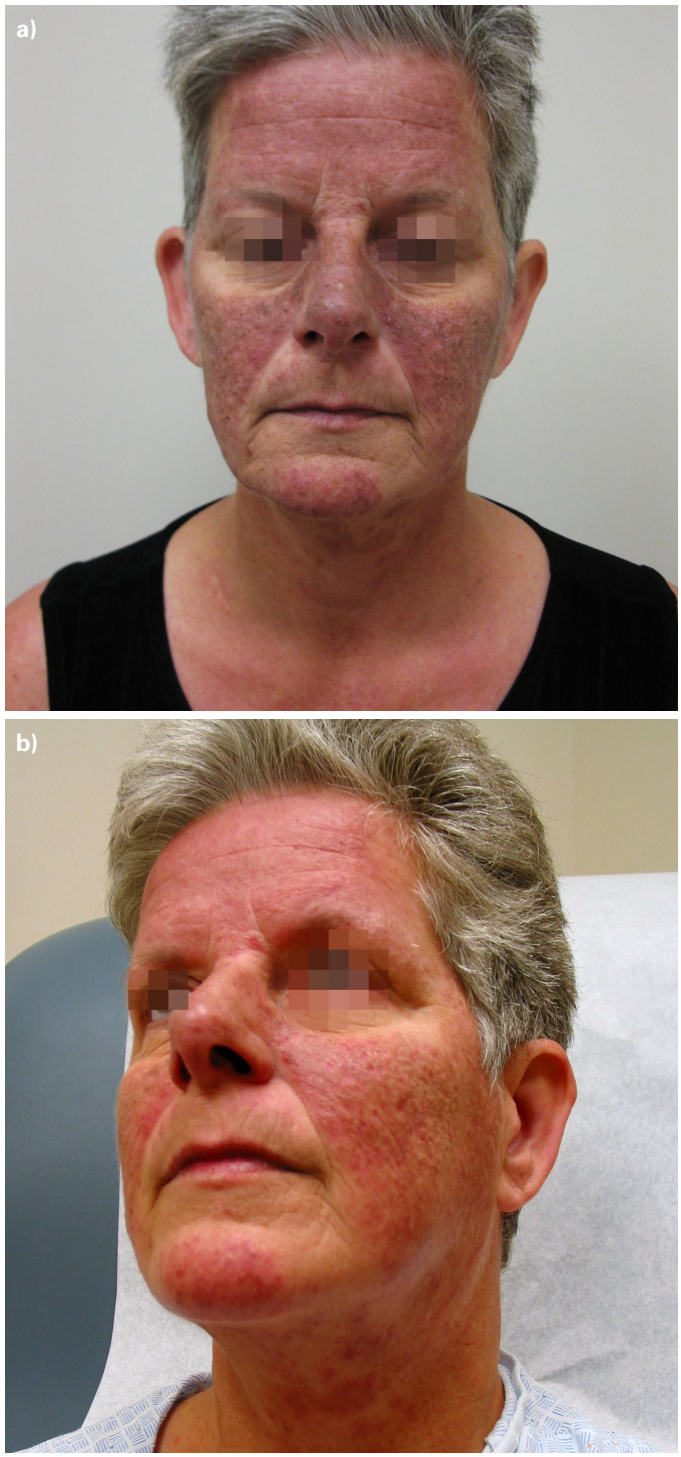
At presentation, the patient had erythematous, crusted patches, papules and small plaques on most of her forehead, nose and cheeks and to a lesser degree on her chin, neck, upper chest and extensor surface of the arms (Figure 2 A-B). The lesions were non-pruritic, non-tender and not painful. Biopsies were obtained from the chest and left upper arm (Figure 3). Both lesions showed hyperkeratosis with focal interface dermatitis with increased dermal mucin, consistent with systemic lupus erythematosus (SLE). An antinuclear antibody titer drawn that day was positive at 1:1280. An SSA/RO antibody titer was also positive at 135. SSB/La and Anti-Jo antibodies were negative. The eruption improved with application of triamcinolone 0.1% cream and continued to resolve following cessation of capecitabine.

DISCUSSION

Capecitabine is a novel oral chemotherapeutic agent with proven efficacy in patients with metastatic breast cancer and colorectal cancer. The drug is converted to 5′-deoxy-5-fluorocytidine in the liver and subsequently metabolized in tissue and tumor first to 5′-deoxy-5-fluorouridime then 5-fluorouracil. Cutaneous side effects of this drug continue to surface as its use in cancer management increases. The dose-limiting side effects most frequently observed with capecitabine are hyperbilirubinemia, diarrhea, and hand-foot syndrome or PPE.[2] According to Cassidy et al, capecitabine has a safety profile superior to 5-FU with a lower incidence of diarrhea, stomatitis, nausea, alopecia, and grade 3 or 4 neutropenia leading to significantly fewer neutropenic fever/sepsis cases and fewer hospitalizations.[1]

Various skin toxicities have been attributed to capecitabine and reported in the literature. PPE is a common adverse reaction to capecitabine, occurring in 50% to 68% of patients.[3] Rarer

FIGURE 2. Parts **a-b)** Clinical photographs of systemic lupus erythematosus on face and upper chest



side effects reported include localized skin hyperpigmentation, onychodystrophy, and stomatitis.[4,5] One case of subacute cutaneous lupus erythematosus has also been reported which occurred in a patient with preexisting positive ANA titers and a positive family history of SLE.[6]

A study of other oral prodrugs of 5-FU such as Tegafur have suggested Anti-SSA/Ro antibody to be a risk factor for drug eruptions.[7] The authors speculate that 5-FU may translocate SSA/Ro antigens to the surface of keratinocytes, leading to a lupus-like eruption.[7] While the mechanism remains unclear, it is evident that capecitabine is responsible for a number of dermatologic side effects.

As use of this drug continues to grow in the fight against metastatic breast, colorectal, and genitourinary cancers, it is important to recognize the breadth of cutaneous clinical presentations of capecitabine side effects. In conclusion, we present a unique case of capecitabine-induced SLE concurrent with PPE successfully treated with cessation of the offending agent and topical triamcinolone applied to affected areas.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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