

Toxic Dermatitis Due to Capecitabine: Presentation of 2 Cases and Literature Review

M. Gutiérrez-Pascual,^a M. Sols-Candela,^a F. Pinedo,^b and J.L. López-Estebanz^a

^aServicio de Dermatología and ^bServicio de Anatomía Patológica, Hospital Universitario Fundación de Alcorcón, Alcorcón, Madrid, Spain

To the Editor:

Capecitabine is a chemotherapeutic agent of the fluoropyrimidine family, indicated in metastatic colorectal cancer and advanced breast cancer. Its main cutaneous adverse effect is hand-foot syndrome (HFS); cases of skin hyperpigmentation, nail changes, and alterations of the

mucosas secondary to this drug have also been reported. Capecitabine is converted to 5-fluorouracil by the enzyme thymidine phosphorylase, which is found in its highest concentration in tumor tissue. The drug is administered orally and its systemic adverse effects are less severe than those of 5-fluorouracil.¹ We present 2 new cases of toxic dermatitis due to capecitabine where, in addition to HFS, there were localized skin hyperpigmentation and marked nail changes.

The patients were 2 men of 53 and 79 years of age, diagnosed with Duke stage III adenocarcinoma of the colon. After laparoscopic sigmoidectomy, they started adjuvant treatment with capecitabine (Xeloda), the first at a dose of 4000 mg/d and the other at 3000 mg/d. The first patient was seen after the third cycle of chemotherapy, with a 15-day history of skin lesions affecting the palms of the hands, with no associated palmar-plantar dysesthesia. On physical examination, we observed brownish macules of 0.3 cm diameter on both palms, associated with marked desquamation, periungual hyperpigmentation, and moderate erythema of the distal phalanges (Figure 1). The second patient reported palmar-plantar erythema and erosions that started after the second cycle of capecitabine. Examination revealed intense palmar-plantar erythrosis



Figure 1. Palmar hyperpigmentation associated with erythema and periungual desquamation.



Figure 2. Plantar erythrosis, onychomadesis, subungual hemorrhages, and erosive periungual vesicular lesions.

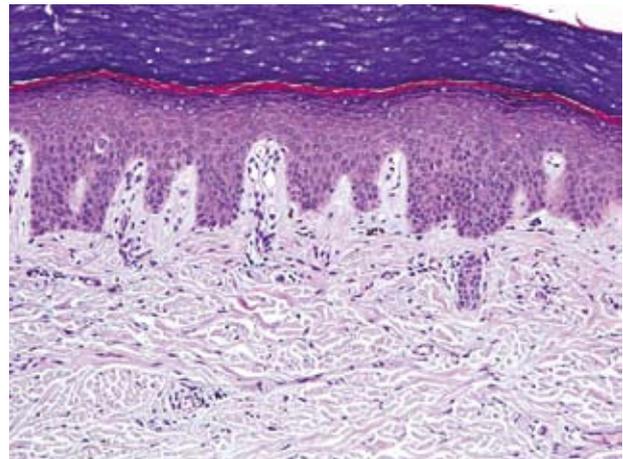


Figure 3. No involvement of the epidermis. Mild dilatation of the superficial vascular plexus and pigment incontinence (hematoxylin-eosin, $\times 100$).

associated with erosive periungual vesicular lesions and marked nail changes (Figure 2). The diagnosis of toxic dermatitis due to capecitabine with associated HFS was confirmed by skin biopsy (Figure 3). Treatment was started with topical corticosteroids and antibiotics; in the first case the dose of capecitabine was reduced to 2500 mg/d and the medication was discontinued in the second. The patients presented a progressive clearing of the skin lesions, with persistence only of mild paronychia and secondary onychodystrophy 4 months later in the second patient.

HFS secondary to capecitabine occurs in 50% to 68% of patients treated with this drug.² It is characterized by palmar-plantar erythema and pain and can lead to the appearance of distal ulcers if the dose of the drug is not reduced or the medication discontinued.³ The pathogenesis is unknown, although 2 theories have been proposed, both of which involve high local concentrations. The first hypothesis is based on the lower concentration of thymidine phosphorylase in the acral tissues, leading to a greater accumulation of the drug at that site. The second hypothesis suggests a greater elimination of the drug through the eccrine glands; as these glands are more concentrated in the palmar and plantar regions, there will also be a greater cumulative dose in these areas.² HFS can occur after the administration of other chemotherapeutic agents, mainly those of the fluoropyrimidine family, such as 5-fluorouracil, the active metabolite of capecitabine.⁴ The 2 patients presented here developed HFS of different severities, mild in the first case and severe in the second. Treatment is symptomatic with emollients and topical corticosteroids; the possibility of combining the chemotherapy treatment with a dihydropyrimidine dehydrogenase inhibitor has recently been proposed, as it appears to reduce the intensity of HFS. Dihydropyrimidine dehydrogenase is responsible for the catabolism of more than 80% of the fluoropyrimidines. If the addition of an inhibitor of this enzyme to chemotherapy treatment reduces the intensity of HFS, it would indicate that a degradation product of the drug is possibly responsible for the HFS.⁵

Other, less common cutaneous adverse effects of capecitabine include mucositis,⁶ onycholysis and onychomadesis,⁷ localized or generalized skin hyperpigmentation,⁸ acral sclerodermiform changes, and acquired palmar-plantar keratoderma.

Hyperpigmentation, which was marked in our first patient, occurs in 3% of patients treated with capecitabine.⁸ The first case was published in 2002,⁹ and the majority of cases have been reported in blacks and Asians; to date, we have only found 2 cases published in white individuals.^{8,10} No histological study was available

in either of those cases, and we were therefore unable to perform comparative studies with the findings in our patient. The causes of hyperpigmentation are unknown, although 2 theories have been proposed: direct stimulation of melanogenesis, and postinflammatory hyperpigmentation.⁸ The fact that histological study in our patient showed pigment incontinence with no increase in the number of melanocytes would support the second hypothesis.

Nail changes caused by the use of capecitabine have hardly been mentioned in the literature. Our search produced only 1 published case⁷; the proposed mechanisms of onycholysis were direct pharmacological toxicity or secondary bacterial or fungal colonization and, in the case of onychomadesis, absent mitotic activity of the nail matrix.

We present 2 new cases of toxic dermatitis due to capecitabine. In addition to the most common skin manifestation, HFS, there were other, very rare cutaneous toxic effects, including localized skin hyperpigmentation and nail involvement. As the use of this chemotherapeutic agent has been increasing recently, we must know of its possible adverse effects in order to improve clinical management.

Correspondence:
Marta Gutiérrez Pascual
C/ Budapest, 1
28922 Alcorcón, Madrid, Spain
mgutierrezp@fhacorcon.es

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Seidman AD. Monotherapy options in the management of metastatic breast cancer. *Semin Oncol*. 2003;30:6-10.
2. Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda). *Eur J Oncol Nurs*. 2004;8:31-40.
3. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome. Insights from clinical trials evaluating capecitabine. *Oncology*. 2004;18:1161-8.
4. Hueso L, Sanmartín O, Nagore E, Botella-Estrada R, Requena C, Llombart B, et al. Eritema acral inducido por quimioterapia: estudio clínico e histopatológico de 44 casos. *Actas Dermosifiliogr*. 2008;99:281-90.
5. Yen-Revollo JL, Goldberg RM, McLeod HL. Can inhibiting dihydropyrimidine dehydrogenase limit hand-foot syndrome caused by fluoropyrimidines? *Clin Cancer Res*. 2008;14:8-13.
6. Bell KA, Perna AG, Hsu S. Mucositis a treatment-limiting side effect in the use of capecitabine for the treatment of metastatic breast cancer. *J Am Acad Dermatol*. 2001;45:790-1.

7. Chen GY, Chen YH, Hsu NM, Tsao CJ, Chen WC. Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol.* 2001;145:521-2.
8. Vázquez-Bayo C, Rodríguez-Bujaldón AL, Jiménez-Puya R, Galán-Gutiérrez M, Moreno-Giménez JC. Hiperpigmentación secundaria a capecitabina. *Actas Dermosifiliogr.* 2007;98:491-3.
9. Pui JC, Meehan S, Moskovits T. Capecitabine induced cutaneous hyperpigmentation: report of a case. *J Drug Dermatol.* 2002;1:202-5.
10. Tavares-Bello R. Capecitabine-induced hand-foot syndrome and cutaneous hyperpigmentation in an elderly vitiligo patient. *J Eur Acad Dermatol Venereol.* 2007;21:1434-5.

Atypical Skin Metastases of Mucinous Adenocarcinoma of the Prostate With Signet Ring Cells

N. López-Navarro,^a J.C. López-Sánchez,^b J.E. Pérez-Enríquez,^c R.J. Bosch,^a and E. Herrera^a

^aServicio de Dermatología, ^bServicio de Anatomía Patológica, and ^cServicio de Urología, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain

To the Editor:

Skin metastases from carcinoma of the prostate are extremely rare. When they occur, they usually appear as multiple nodules in the suprapubic area or on the anterior aspect of the thighs. The appearance of distant lesions, outside the typical areas, is uncommon, with only 14 reports in the past 25 years. We report a case with an atypical presentation of skin metastases from adenocarcinoma of the prostate, also highlighting the utility of prostate specific antigen (PSA) as an immunohistochemical marker in skin metastases of unknown origin in elderly men.

The patient was a 62-year-old man who developed multiple nodular lesions on the thorax, axillas, and face; the lesions had developed over the previous 3 months. They were particularly numerous on the face, especially on the right side, extending towards the scalp (Figure 1). Associated symptoms included a 4-month history of dyspnea on exertion and costal pain on deep inspiration,



Figure 1. Multiple nodular lesions on the face.

together with difficulty urinating over the past 2 years. With a clinical suspicion of skin metastases, biopsy was performed of 1 of the lesions on the thorax. Histological study revealed a well-defined, dermal tumor nodule that did not reach the epidermis. It was formed of undifferentiated epithelioid cells, arranged in cords, and with signet ring morphology (Figures 2A and 2B). These cells were surrounded by a mucinous stroma (Figure 2C). Immunohistochemical analysis was intensely positive for cellular adhesion molecule 5.2 and PSA (Figure 2D). In view of the results obtained up to that time, additional tests were performed that focused particularly on the prostate; these tests had the following main findings: normocytic anemia, PSA of 3901 ng/mL, bilateral basal interstitial-alveolar infiltrates on the chest x-ray, and a thoracoabdominopelvic computed tomography showing thickened, irregular walls of the bladder; right paratracheal, subcarinal, para-aortic, and interaortocaval lymph nodes; and blastic bone changes, compatible with a metastatic pattern. On rectal examination, the prostate was found to be increased in size with no sulcus; it was poorly defined, fixed, and had palpable, stony-hard nodules in both lobes. Prostatic biopsy revealed adenocarcinoma affecting 90% of each lobe (Gleason score, 8). It was particularly noticeable that the histology of the primary tumor was similar to that of the skin metastases, with signet ring cells surrounded by a mucinous stroma. In view of the advanced stage of the disease, it was decided to administer palliative treatment with the gonadotropin releasing hormone analogue, goserelin, 10.8 mg subcutaneously every 3 months. The patient presented a progressive reduction in the number of skin lesions over the following months.

Skin metastases from internal tumors are uncommon in clinical practice. In women, the most common origin of skin metastases is adenocarcinoma of the breast, whilst squamous cell carcinoma of the lung is the most common