Letter to the Editor

Title: Capecitabine-induced eruptive acral hyperpigmentation: clinical and dermoscopic evaluation of two cases.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dth.12853

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Running head: drug-induced acral hyperpigmentation

Keywords: capecitabine, hyperpigmentation, dermoscopy

Conflict of interest Disclosures: none declared

Funding source: none

Editor,

In the last decades new chemotherapeutic drugs and new protocols have significantly improved the survival rate of oncologic patients. However, a large variety of side effects can occur and skin is one of the most commonly involved body sites. Skin toxicity is generally not life threatening, but may significantly affect quality of life (Lou et al, 2016). Capecitabine is an oral chemotherapeutic agent, currently used in the treatment of locally advanced or metastatic breast cancer and for colorectal cancer as first line and in adjuvant setting; furthermore, it has largely replaced the use of 5-fluorouracil (5-FU) for several indications, including gastric cancer (Caprez et al, 2018). Capecitabine is well known for potentially inducing skin toxicity, which mainly appears as acral hyperpigmentation, sometimes associated with loss of fingerprints, and hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia (Villalón et al, 2009; van Doorn et al, 2017; Tognetti et al, 2015).

We report two cases documented by means of dermoscopy of capecitabine-induced acral hyperpigmentation. The first patient was a Caucasian woman in her 50s (photo-type II) who developed multiple eruptive and asymptomatic acral macules, after two weeks of capecitabine administration for gastric cancer. Clinically, lesions appeared as sub-centimetric brown macules, located on soles bilaterally with a symmetrical distribution. **Fig.1** On dermoscopic examination, a parallel ridge pattern was the hallmark in all lesions, mimicking acral melanoma; notably eccrine glands were spared from pigmentation. Five months after last capecitabine administration, a complete resolution was observed. The second patient was a Caucasian woman in her 40s (photo-type III), affected by breast cancer and treated with capecitabine and denosumab. She was referred to our dermatologic department for the sudden

appearance of multiple asymptomatic brown-pigmented macules on her soles. On clinical examination, we observed bilateral brownish macules on plantar region. Upon dermoscopy all macules showed lattice-like and parallel ridge pattern, mimicking acral melanocytic nevi; one large lesion referred to a congenital nevus was present and not affected by the therapy **Fig.2** Capecitabine is an oral precursor of 5-fluorouracil (5-FU) which is converted to 5-FU in tumor cells by the enzyme thymidine phosphorylase; this conversion improves the ability of the drug to target cancer cells. Cutaneous adverse events represent the most common side effects related to capecitabine administration; they generally occur after few weeks of treatment and mainly consist of HFS syndrome and hyperpigmentation. The pathogenesis of these conditions is not clear; it has been hypothesized that capecitabine may cause these side effects through mitochondrial dysfunction, inducing keratinocytes apoptosis. Another hypothesis may be linked to small vessels local trauma from the mechanical stress of daily activities. In addition, capecitabine elimination through the eccrine glands, which are predominantly located on palms and soles, may also play a role (Caprez et al, 2018; Villalón et al, 2009).

In literature, hyperpigmentation caused by capecitabine has been mainly reported in subjects with photo-type IV and V, but rare cases have been observed in fair skin individuals (photo-type II and III) (Lallas et al, 2015). Concerning the differential diagnosis, even though the clinical and dermoscopic aspect may simulate acral melanocytic lesions (both nevi and melanomas), the sudden appearance, as well as the presence of multiple lesions and the association with capecitabine administration, usually allow to make the correct diagnosis without performing a biopsy. Other differential diagnosis to consider are subcorneal

hemorrhages and exogenous pigmentations (Tognetti et al, 2015). Notably, in our cases, dermoscopy revealed a parallel ridge pattern that is mainly related to melanoma diagnosis on acral sites (Lallas et al, 2015). However, in capecitabine-induced hyperpigmentation, eccrine glands were clearly visible and this is a relevant criterion to discriminate between a melanoma and not melanocytic proliferation. For these reasons, in presence of multiple eruptive hyperpigmented macules involving the acral area, a drug-induced origin should be always taken into account, even in fair-skin individuals, in order to avoid unnecessary biopsies in fragile oncologic patients.

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Figure legends

Figure 1. (a) Hyperpigmented macules (black arrows) located on soles bilaterally occurring during capecitabine administration. (b, c) Dermoscopy of the same lesions with parallel ridge pattern and sparing of eccrine glands visible. (d) Clinical resolution of the lesions after treatment discontinuation.

Figure 2. (a) Clinical manifestations of eruptive pigmentations (black arrows) due to capecitabine intake on patient's soles, especially on left one. (b) Parallel ridge and (c) lattice-like pattern upon dermoscopic evaluation. Notably, eccrine glands were clearly visible.