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Capecitabine-induced stomatitis: a likely pathogenetic mechanism of oral lichenoid mucositis

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Sirs:

Capecitabine is an oral prodrug that is converted to only one active metabolite, fluorouracil (5-FU), which is used to treat numerous types of neoplasms, such as those of the breast, esophagus, and larynx cancer, as well as metastatic breast cancer as either a single agent or in combination with docetaxel after the failure of prior anthracycline-based chemotherapy [1]. The Federal Drug Administration has recently approved the combination of capecitabine and lapatinib for the treatment of advanced or metastatic breast cancer overexpressing human epidermal growth factor receptor-2 [2].

We treated a 61-year-old female patient with breast cancer who, following a right mastectomy, homolateral axillary lymphoadenectomy, and radiotherapy, entered into remission. After 7 years of remission, metastatic progression of the disease was determined, and the patient received radiotherapy and anthracycline-based chemotherapy, which were only partially successful. A drug regimen of lapatinib

[1250 mg daily oral dose (PO qd)] continuously plus capecitabine (2000 mg/m² PO qd) for a 14-day cycle with 7 days off [3] and, concurrently, zoledronic acid (4 mg intravenous monthly) and lansoprazole (15 mg PO qd) was subsequently administered.

During the third cycle she developed a mild palmar-plantar rash that disappeared spontaneously within 24 h. During the fourth cycle she developed a persistent and painful lichenoid mucositis with bullous areas localized on the anterior third of the tongue (Fig. 1a), which that showed a positive Nikolsky's sign, as well as erythematous areas on the cheeks bilaterally (Fig. 1b), accompanied by a severe hand-foot syndrome (HFS). Due to this last grade 3 side effect, the patient was placed on dechallenge and rechallenge for a fifth cycle at a dosage of capecitabine adjusted to 50% [4]. The oral lesions disappeared, while the HFS presented with a milder clinical aspect (grade 1). The patient was not considered to be definitively dechallenge because the discomfort of the skin lesions did not interfere with her normal daily activities and quality of life.

Oral biopsy revealed hyperparakeratosis, focal hypogranulosis, intraepithelial necrotic keratinocytes, and some angiectatic vessels in the lamina propria with focal lymphomonocytic infiltrate (Fig. 1c, d). In order to establish a proper diagnosis and exclude a paraneoplastic and/or drug-induced disease, we performed direct immunofluorescence, indirect immunofluorescence, immunoblotting and enzyme-linked immunosorbent assay (ELISA) tests for desmogleins 1 and 3 and for BP230 and BP180. The results for all tests were negative.

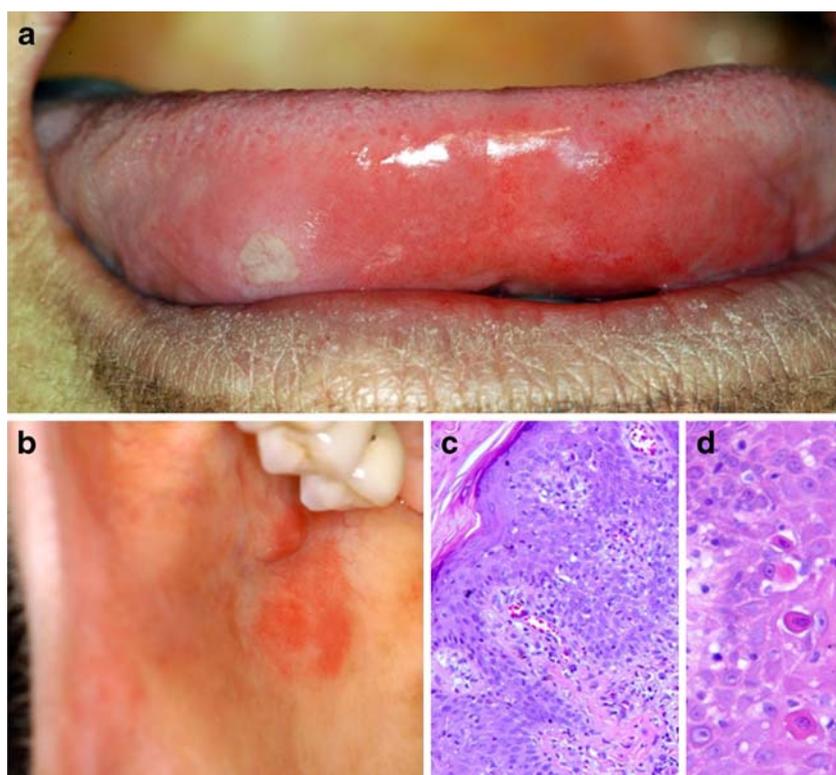
We obtained a score of 6 on the Naranjo adverse drug reaction (ADR) probability scale [5], indicating that capecitabine was the "probable" cause of the HFS and

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Fig. 1 **a** Lichenoid lesions with bullous areas localized at the anterior third of the tongue, **b** an erythematous lesion of the right cheek. **c** Histology from oral mucosa revealed hyperparakeratosis, focal hypogranulosis, intraepithelial necrotic keratinocytes, and some angiectatic vessels in the lamina propria with focal lymphomonocytic infiltrate (hematoxylin and eosin; original magnification $\times 10$). **d** Higher magnification better highlights some intraepithelial necrotic keratinocytes (hematoxylin and eosin; original magnification $\times 20$)



oral mucositis. No other side effect or hematological abnormalities, except for a mild anemia and neutropenia, were detected. Given this score as well as the fact that the dosage of lapatinib was maintained constant, while the dosage of capecitabine was reduced, we diagnosed capecitabine-induced lichenoid stomatitis.

To the best of our knowledge, this is the first reported case in which the oral clinical aspects of capecitabine-suspected oral mucositis toxicity, characterized by lichenoid lesions with bullous and erythematous areas, are described. Due to the mild form of this side effect, our patient did not receive any systemic treatment; however, she was given topical corticosteroids, i.e., betamethasone (2 mg dissolved in 75 cc of water to be used as mouthwash) and a solution of chlorhexidine 0.12% as mouthwash twice a day for 7 days.

Although the frequency of grade 3/4 toxicities occurring with capecitabine alone or in combination with lapatinib has been reported to be very low (0–1%), the oral adverse event described as stomatitis and/or mucositis [6, 7] occurs at a frequency of 11–15% (all grades) [2, 3].

The pathogenetic mechanism underlying stomatitis is still largely unknown. As in the case of HFS [8], it is likely that it may be due to a toxic effect on the basal keratinocytes and upper corion microvassels. Indeed, as in the skin condition [9], the enzyme thymidine phosphorylase (TP) may be present in the oral keratinocytes where it

converts 5-FU into a false nucleotide (fluorouridine triphosphate) instead of thymidine, thus inhibiting DNA synthesis and causing a subsequent apoptosis [1]. The expression of TP may be upregulated and, therefore, the elevated rate of TP in the oral keratinocytes may foster an accumulation of metabolite, resulting in cytotoxicity [4, 10]. Conversely, other studies have shown conflicting results about the role of the enzyme dihydropyrimidine dehydrogenase (DPD), with some showing that a high expression of DPD may enhance the production of 5-FU catabolites, with a subsequent increase of cell toxicity [10], and others showing that DPD activity has a negligible cytotoxic effect on human keratinocytes [11]. In addition, the damage to the upper corion vessels may be fostered indirectly through the inhibition of angiogenesis via the induction of thrombospondin-1 [12].

Lastly, 5-FU influences salivary excretion by decreasing the salivary flow rate—not only due to simple passive diffusion but also by an active process—thus fostering the development of oral mucositis [13]. Nevertheless, further evidence is required to support these hypotheses.

Conflict of interest The authors have no conflict of interest to declare

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