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ORIGINAL ARTICLE

Oral hyperpigmentation as adverse effect to capecitabine

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Abstract:

Capecitabine (Xeloda®) is an antineoplastic drug normally used as adjuvant chemotherapy for metastatic colorectal and breast cancer. A common adverse effect of capecitabine is hand and foot syndrome (HFS), a condition that, although not life threatening, can reduce drastically quality of life and result in patient withdrawal from treatment. Palmoplantar hyperpigmentation is a condition that has been found as the initial manifestation of HFS in most patients. The association of palmoplantar and oral hyperpigmentation as an adverse effect to capecitabine has rarely been described in the literature. We report a case of oral and palmoplantar hyperpigmentation in a 61-year-old woman receiving capecitabine for metastatic colon cancer. At the chemotherapy 2nd cycle, the patient referred burning mouth, and clinical inspection revealed brownish spots measuring between 2 and 10 mm, in addition to similar hyperpigmentated macules in palms and soles of feet, both asymptomatic. A 7-month-follow-up, still under chemotherapy with oral Xeloda®, showed regression of mouth manifestations while the palmoplantar spots intensified, with progression of dryness and tingling. This report highlights the importance of early diagnosis of HFS through the oral hyperpigmentation, which is a manifestation easily detectable by the dentist.

Keywords: Capecitabine, Hyperpigmentation, Mouth Mucosa, Drug-Related Side Effects and Adverse Reactions

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INTRODUCTION

Capecitabine is an oral antineoplastic prodrug, converted to 5-fluorouracil (5-FU) in the body, which was approved by the U.S. Food and Drug Administration (FDA) in 1998. It has been widely used for fluoropyrimidine-sensitive diseases, being the first line treatment for metastatic colorectal cancer, besides colon and metastatic breast cancers[1].

A common, dose-limiting, adverse effect of capecitabine is hand and foot syndrome (HFS), a condition that can be classified into three grades according to the intensity of the symptoms: Grade 1: Dysesthesia or paresthesia, erythema and swelling; Grade 2: Pain and discomfort affect the daily activities; Grade 3: Blistering, moist ulceration and desquamation, and severe pain. However, palmoplantar hyperpigmentation has been suggested by many authors to be included in Grade 1 HFS, since it has been found as the initial manifestation in most patients rather than erythema, besides camouflaging classical signs and symptoms of HFS[2-4].

Although not being life threatening, HFS can reduce drastically quality of life and result in patient withdrawal from treatment, and its early detection allows choosing between appropriate dose reduction or modification of chemotherapy regimens, which can avert the discontinuation of the treatment[5]. The association of palmoplantar and oral hyperpigmentation as an adverse effect to capecitabine has rarely been described in the literature[1].

The aim of the present manuscript is to report a case of early detection of HFS through an oral manifestation, in a 61-year-old woman receiving capecitabine for metastatic colon cancer.

CASE PRESENTATION

A 61-year-old woman was referred for dental evaluation. She was being submitted to chemotherapy for a colon cancer with ovarian metastasis. At anamnesis, she referred burning sensation in tongue and lips, especially during teeth brushing and having soft drinks. Hemogram revealed normal value ranges.

The physical examination revealed spots of brownish hyperpigmentation measuring between 1 and 5 millimeters on jugal mucosa and right border of tongue (Figures 1 and 2), and between 1 and 10 millimeters on palms and soles of feet, asymptomatic (Figures 3 and 4). At that moment, she was at the 6th day of the 2nd cycle of Xeloda® (F Hoffmann-La Roche, Basel, Switzerland) oral

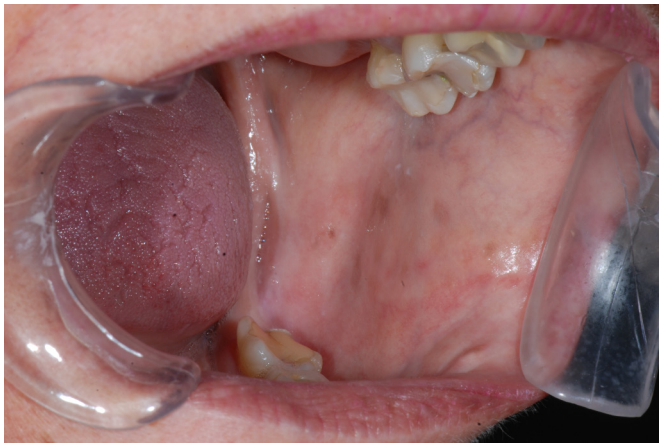

Figure 1. Discreet brownish spots measuring between 1 and 5 millimeters on jugal mucosa.

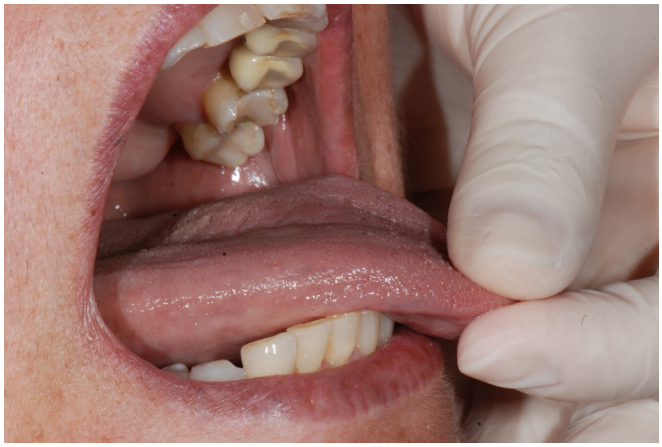

Figure 2. Brownish spots on the right border of the tongue.

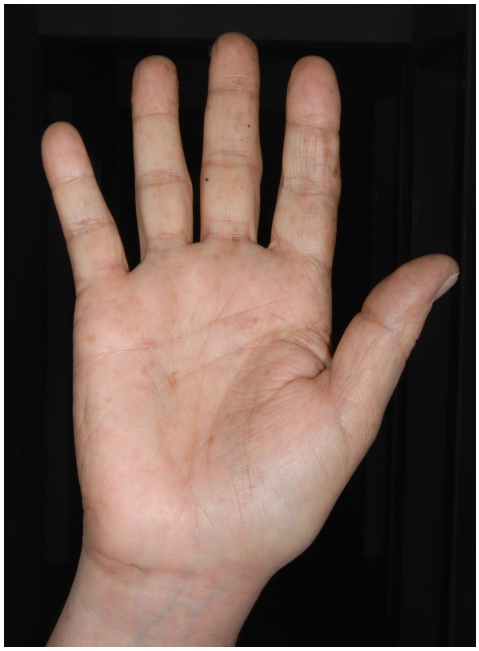

Figure 3. Similar spots measuring between 1 and 10 millimeters on palms.

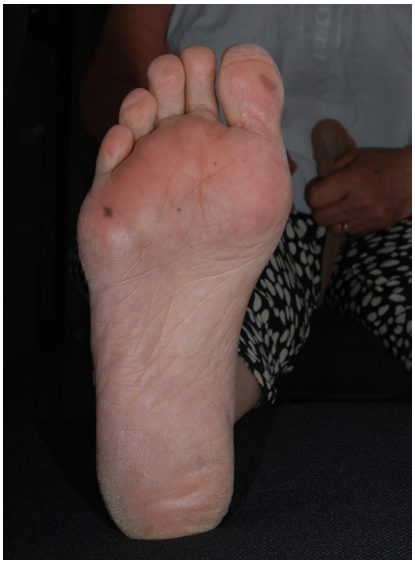

Figure 4. Mild dryness and brownish spots on soles of feet.

intake. The cycles had a 7-days duration, with a 21-days frequency. She had noticed the spots in the soles of feet and palms before dental assessment, but not the ones in the mouth. The correlation of clinical data leaded us to the diagnostic of oral hyperpigmentation as adverse effect to capecitabine.

It was prescribed lanolin based lip balm, besides artificial saliva and toothpaste without sodium lauryl sulfate[6,7]. After a 7-months follow-up, still under treatment with Xeloda®, the patient returned referring some relief of the oral symptoms and showing a smoothing of the macules in oral mucosa (Figures 5 and 6). Conversely, soles of feet and palms showed more intense spots and got erythematous, tingling and strongly dry (Figures 7 and 8). Moisturizer for hands and feet were prescribed, and the lanolin based lip balm and artificial saliva were maintained. The patient has not finished the capecitabine treatment yet. Therefore, she is kept under a close follow-up.

DISCUSSION

The fluoropyrimidine 5-fluorouracil (5-FU) is the most extensively used chemotherapeutic agent in the treatment of metastatic colorectal cancer for many years. To guarantee a safer and more effective treatment, prodrugs of 5-FU have been created such as capecitabine[8].

Xeloda® is an antineoplastic drug orally administered, normally used as adjuvant chemotherapy for metastatic colorectal, breast and gastric cancers. It is converted to 5-FU in the tumor tissue, process mediated

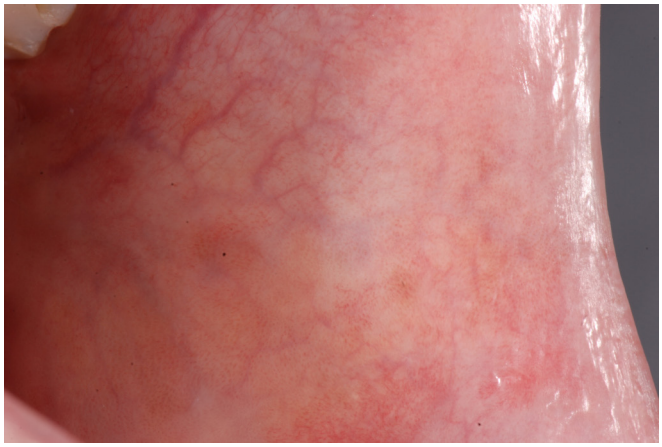

Figure 5. Jugal mucosa showing smoothing of the macules after 7-months under treatment with Xeloda®.

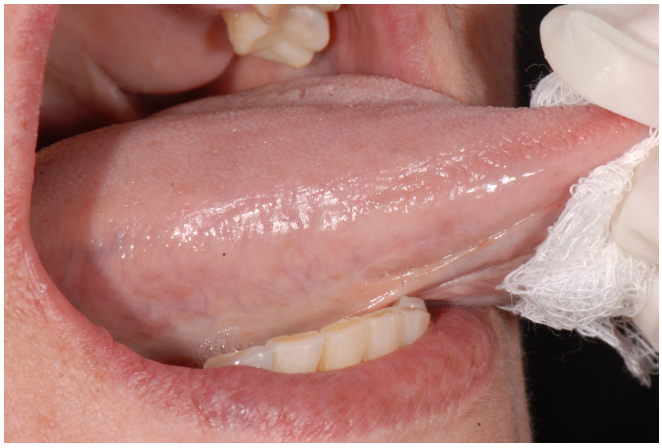

Figure 6. Smoothing of the macules on the border of the tongue.

by thymidine phosphorylase. The oral intake ensures continuous exposure to 5-FU, without the need for a central venous access, and meets the patient's preference for oral treatment instead of endovenous[9,10].

The most common dose-limiting adverse effects of capecitabine include nausea, vomiting, diarrhea, hyperbilirubinemia, bone marrow suppression and HFS[11-13]. HFS, also known as palmar-plantar erythrodysesthesia, is characterized by tingling and dysesthesia of the palms and soles of the feet, which may progress to burning pain with diffuse erythema and swelling and, in severe cases, result in blistering, scaling and erosions or ulcerations of the skin. In advanced cases, the pain may interfere in quality of life, impeding daily activities. In such situation, dose adjustment or even patient withdraw from treatment may be consider[5].

Among the skin manifestations of HFS, capecitabine-induced skin pigmentation may occur. Although it is not well established whether

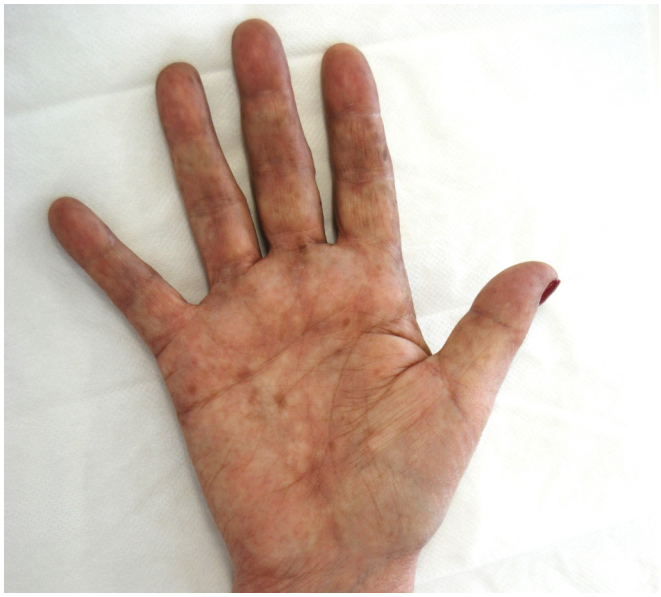

Figure 7. As opposed to the mouth, palms showed more intense spots.

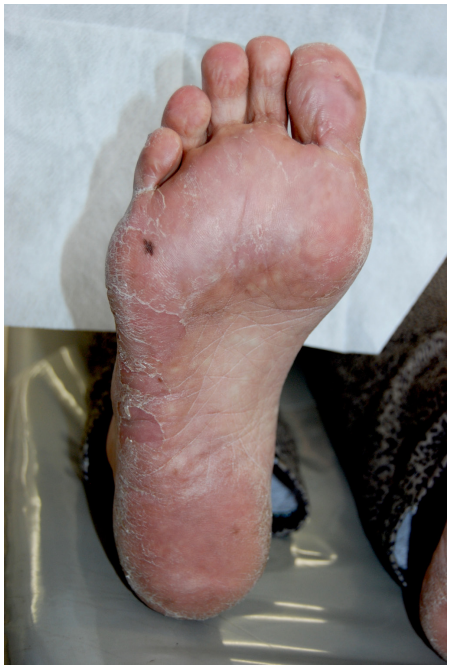

Figure 8. Soles of feet also showed more intense spots and got erythematous and strongly dry.

hyperpigmentation is a separate toxicity or part of grade 1 HFS, it may be an indicator of toxicity development and predict a dose adjustment necessity[14]. The combination of oral mucosa and palmar-plantar hyperpigmentation has rarely been described[1,15,16].

The patient in this case report was already at the 2nd cycle of Xeloda® when admitted to dental service, which impeded prior evaluation of the lesions. At that moment, she referred burning sensation in tongue and lips, but didn't had noticed the 1-5 mm spots on bilateral jugal mucosa and right border of tongue, as opposed of that on palms and soles of feet, where she had already noticed.

After a 7-month-follow-up, still under treatment, the oral signs and symptoms presented discrete regression. At the same manner, the patient of Villalón's study[16] was showing several small (1–5 mm) pigmented brown macules on her face, hands, palms, soles and tongue in her fourth cycle of chemotherapy with capecitabine. This finding is also in agreement with the report of Vasudevan[1], where HFS and oral pigmentations occurred after two cycles of capecitabine, and regressed when the treatment completed.

Table 1 shows the main aspects of the most recent case reports in the literature of capecitabine oral intake and oral side effects comparing gender, age, ethnicity, diagnosis, oral manifestation and its symptoms, and the established treatment (Table 1).

Owing to the patient story of capecitabine use, besides the benign appearance of the lesions, biopsy was judged not necessary, and a close follow-up was chosen instead. Other case reports of patients receiving capecitabine showed lentigo-maligna-like, melanocytic nevi, atypical nevi-like or lentiginous melanocytic lesions, and the its fadedness suggests a more lentiginous melanocytic feature of the lesion[16]. Dermoscopic exams from acral hyperpigmentated lesions use to be confusing[17]. On the other hand, Villalón et al.[16] indicate dermoscopy to avoid unnecessary biopsies. Nevertheless, suspicious lesions should always be removed.

The patient showed a worsening of symptoms in hands and feet over time, while mouth's burning sensation got softened instead. It is not established whether the introduction of oral care with lanolin based lip balm, artificial saliva and toothpaste without sodium lauryl sulfate was responsible for improving the patient's oral clinical status. Palms and soles of feet were asymptomatic at the beginning of the treatment with capecitabine, when there were only the brown macules, however, with the passage of the months they became erythematous, tingling and strongly dry. This finding supports the theory that oral or skin hyperpigmentation is an important clinical sign of impending capecitabine toxicity[14].

Oral hyperpigmentation is a capecitabine-induced manifestation easily detectable by the dentist, which usually manifest at the beginning of the

treatment. Despite the lack of consensus whether hyperpigmentation would be considered part of HFS or not, we suggest that this finding should be considered an important clinical sign of imminent drug toxicity, thus, it should warn to consider reducing the capecitabine dose or even its discontinuation, besides a patient's close monitoring. More studies are demanded to help to determine the meaning of oral hyperpigmentation in capecitabine toxicity.

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