

## Pigmented Lesions of Buccal and Labial Mucosa in a Patient Treated by Capecitabine (Xeloda): A Case Report

Talia Becker\*

Department of Oral Medicine and Oral Pathology, the Maurice & Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel

**Corresponding author:** Dr. Talia Becker, Department of Oral Medicine and Oral Pathology, the Maurice & Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Israel, Tel: +972-50-5808886; **E-mail:** [becktalia@gmail.com](mailto:becktalia@gmail.com)

**Received date:** 02 February, 2015; **Accepted date:** 26 March, 2015; **Published date:** 31 March, 2015.

**Citation:** Becker T (2015) Pigmented Lesions of Buccal and Labial Mucosa in a Patient Treated by Capecitabine (Xeloda): A Case Report. Int J Dent Oral Health, Volume1.1: <http://dx.doi.org/10.16966/2378-7090.106>

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**Keywords:** Capecitabine, Hyperpigmentation, Buccal, Labial

### Introduction

One of the most common adverse reactions associated with usage of the chemotherapeutic oral prodrug capecitabine is Hand-foot syndrome (HFS) identified by hyperpigmentation of hands and feet, which is considered as the initial manifestation of this syndrome. The sudden appearance of multiple melanocytic lesions in patients undergoing chemotherapy with capecitabine, in sites other than hands and feet, has been previously described on the skin of the ear and neck [1] and the mucosa of tongue [2].

Although mucosal focal pigmentation on the tongue has been described in combination with palmar-plantar associated pigmented lesions [2-4], the involvement of buccal and labial mucosa has not been yet reported following initiation of chemotherapy with capecitabine.

We describe the pigmented lesions of buccal and labial mucosa in a 67 year-old patient diagnosed with breast carcinoma and treated by capecitabine.

### Case Report

A 67-year-old Caucasian female, diagnosed in 2006 with breast carcinoma, was referred by her physician to the Department of Oral Medicine of Tel Aviv University with complains of sudden manifestation of oral pigmentation. The patient underwent right breast surgery and axillary lymph node dissection five years earlier, that was followed by radiotherapy and a recommendation for capecitabine tablets as an adjuvant therapy. Capecitabine (xeloda) 1350 mg twice a day for two weeks was recommended, followed by one week treatment-free. After using Capecitabine for four years, pigmented oral lesions were observed in the buccal and labial mucosa within a routine dental examination and she was referred for further evaluation. On clinical examinations of the oral cavity, three pigmented lesions were noted one in the left labial mucosa (Figure 1) and two in the right buccal mucosa (Figure 2). Two months later, the lesions became somewhat darker (Figures 3 and 4). Although the patient was scheduled for a biopsy, unfortunately she had passed away due to her illness.

There was no history of smoking and ACTH hormone levels tested in order to rule out Addison disease were non-contributory.

### Discussion

Capecitabine is an oral prodrug that is converted to its active metabolite, Fluoro-uracil (FU), by the enzyme thymidine phosphorylase. The unique

tumor-selective conversion of capecitabine to active 5-FU is achieved by a 3-step enzymatic process. The enzyme thymidine phosphorylase is found at higher levels in cancer cells compared with its levels in normal tissues cells. As a result, more of the active anticancer agent 5-FU is produced precisely in sites where it is needed; within cancer cells rather than in healthy tissues [5]. Oral capecitabine is being increasingly accepted into clinical practice as it permits convenient administration in a home-based setting. Capecitabine tablets are taken orally twice daily approximately 12 hours apart for 2 weeks followed by a 1-week, treatment-free period [6]. One of the most common adverse events associated with its use in clinical trials and in clinical practice is HFS, also known as palmar-plantar erythrodysesthesia, which is not life-threatening; However, HFS can significantly interfere with the activities of normal daily living [6]. HSF is classified into three grades: Grade 1 consists of limited erythema with swelling, dysesthesia or paresthesia, Grade 2 is a progression of the previous stage where pain and discomfort affect the daily activities of the patient, and Grade 3 is the superimposition of blistering, moist desquamation and ulceration, coupled with severe pain [4]. However, hyperpigmentation of hands and feet, rather than erythema are well thought-out as the initial manifestation in most patients and are considered by many authors as Grade 1 HFS [7,8].

Various theories exist regarding the etiopathogenesis of HFS. One theory involves increased expression of thymidine phosphorylase, which converts capecitabine to active 5-FU in keratinocytes leading to inflammation [9]. Another hypothesis is that hyperpigmentation is related to an increased collection and secretion of the drug by sweat glands which are highly concentrated on the palms and soles [10]. HFS may also be caused by products of dihydropyrimidine dehydrogenase (DPD)-initiated catabolic degradation of 5-FU (4). Stressful situations



**Figure 1:** One pigmented lesion on the left labial mucosa was found on the patient's first physical examination.



**Figure 2:** Two pigmented lesions on the right buccal mucosa were found on the patient's first physical examination.



**Figure 3:** One pigmented darker lesion on the left labial mucosa was found on the patient's follow-up two months later.



**Figure 4:** Two pigmented darker lesions on the right buccal mucosa were found on the patient's follow-up two months later.

such as chemotherapy may allow the deregulation of the melanoma growth stimulating activity (MGSA) gene in melanocytes, leading to the expression of MGSA, MGSA messenger RNA, or MGSA protein, thereby stimulating the differentiation, growth, and development of melanocytes into normal or atypical nevi [11].

The differential diagnosis for pigmented oral lesions may include: physiologic pigmentation, pigmentation associated with systemic disease, postinflammatory pigmentation, oral melanotic macules, melanocytic nevi, amalgam tattoos, oral melanoacanthosis, vascular lesions, Kaposi sarcoma (KS), malignant mucosal melanoma and medication-related pigmentation [12]. Drugs such as Minocycline, antimalarial drugs (including chloroquine, hydroxychloroquine, amodiaquine and

quinacrine), Clofazimine, Zidovudine, methylodopa, oral contraceptives and hormone replacement therapy may cause oral mucosal pigmentation if the breakdown product of the drug itself is pigmented, or if the drug or its metabolite chelates to iron or induces melanin deposition [13]. Chemotherapeutic agents may cause extensive cutaneous pigmentation, however, pigmentation of the oral mucosa has only rarely been documented [2-4,14].

Since the current patient was Caucasian and since she had never smoked, the possibilities of physiologic pigmentation or smoker melanosis were excluded.

The present report is, to our best knowledge, the first case presented with buccal and labial pigmentation in probably associated to the administration of capecitabine. The uncertainty whether hyperpigmentation is a part of the HFS or a separate clinical finding is yet to be determined [4].

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