# Hand-foot Syndrome Due to Capecitabine: Report of Two Cases

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Abstract: Capecitabine is one of the most common chemotherapy drugs known to cause hand-foot syndrome (HFS). It is indicated as adjuvant therapy for the treatment of colorectal cancer, first-line therapy in metastatic colorectal cancer, and as monotherapy or in combination with docetaxel in metastatic breast cancer. Although considered to be safe, it has some adverse effect, such as HFS, which is a localized skin eruption associated with the initiation of therapy with certain chemotherapeutic agents. It is considered common and mild thus frequently but improperly self-managed and impaired quality of life. A fifty seven years old woman on treatment with capecitabine for breast cancer and a 46-years-old woman on treatment with capecitabine for breast and thyroid cancer presented with dry and fissured skin on both palms and soles. They also noted pain and discomfort while doing their daily activities. On examination, there were multiple erythematous-hyperpigmented plaques, with scales and fissures overlying it on both palms and soles. Both patients were diagnosed with hand-foot syndrome due to capecitabine and responded well to topical emollients and steroid

## 1 INTRODUCTION

Hand-foot syndrome (HFS), also known as palmoplantar erythrodysesthesia (PPE) or acral erythema, is a localized skin eruption associated with the initiation of therapy with certain chemotherapeutic agents. It is considered a subtype of toxic erythema of chemotherapy. The clinical presentation of HFS is characterized by a prodrome of dysesthesia followed by the development of painful, symmetrical edema and erythema of the palms, digits, and soles that may evolve into blisters and erosions (Hoesly et al., 2011). Although HFS is considered to affect quality of life, it is not a life-threatening condition and rarely need hospitalization. The incidence of HFS depends on the drug therapy, dosage, and the manner in which the drug is administered (Farr & Safwat, 2011).

The mechanism of HFS remains unclear. Based on experience, HFS is considered to be dose-dependent and probably related to drug metabolite accumulation in the skin (Farr & Safwat, 2011). Discontinuation of the offending agent generally leads to skin regeneration over 1-2 weeks (Abushullaih, 2002).

Some risk factors were identified to develop HFS, including the type, dose and duration of chemotherapy being used and this risk increases with each dose of potential HFS inducing chemotherapy. Other risk factors include advanced age, female, performance status, and exposure to total body irradiation (Farr & Safwat, 2011; Lassere & Hoff, 2004).

Capecitabine is one of the most common chemotherapy drugs known to cause HFS. Other drugs are 5-fluorouracil and liposomal doxorubicin. Capecitabine is a fluoropyrimidine with antineoplastic activity. It is a systemic prodrug of 5-fluorouracil, which has advantage of being orally administered and has better safety profile (Gressett, 2006). Currently, it is indicated as adjuvant therapy for the treatment of colorectal cancer, first-line therapy in metastatic colorectal cancer, and as monotherapy or in combination with docetaxel in metastatic breast cancer. Although it is considered to be safe, capecitabine has side effects, such as nausea, vomiting, diarrhea, stomatitis, and most commonly, hand-foot syndrome. This condition is considered mild thus frequently self-managed, instead of being referred to Dermatologists. However, the management is somewhat not proper and the condition can be worsening and further impaired the patient's quality of life. This function impairment is the main criteria in HFS severity classification. We report two cases of hand-foot syndrome due to



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capecitabine managed with topical emollients and steroid.

## 2 CASE

First patient is a 57-years-old woman who was consulted by Surgery Outpatient Clinic with right breast cancer TxNxM1 and dry skin on July 12th 2017. She came to our clinic with chief complaints of dry and fissured skin, accompanied with pain on both palms and soles since 1 year ago and got worsen since. Capecitabine was taken daily since 1 year prior to admission and 8 months ago she had mild redness, dry, and flaky skin on both palms. However, it did not impair her activities.

One month ago, she developed peeling of skin and itch over both palms and soles. She overcame it by rubbing skin with baby soap bar and warm water but the condition didn't improve. Two weeks ago, the skin peeling worsen and accompanied by pain everytime she walks or holds things.

History of contact with irritants, such as detergents and dishwasher soap, was admitted but she denied the usage of new brands or products. No history of atopic and allergy were recorded on patient, as well as on patient's family. She bathes twice a day with bar soap and regular temperature water. Patient is planned to receive capecitabine for 6 more months.

On September 2012, patient was diagnosed with right breast tumor suspect of malignancy and referred to Cipto Mangunkusumo Hospital and then underwent modified radical mastectomy of the right breast. She started 25 radiotherapy sessions on July 2013 and 6 cycles of adjuvant chemotherapy on November 2013. During that time, her laboratory result showed bicytopenia (anemia and leukopenia) with normal liver function, and normal renal function (on August 2014, her estimated glomerular filtration rate was 84.4 mL/min/1.73m$^2$).

In 2015, multiple metastatic nodules on both lungs were detected through chest radiography and multiple slice CT scan (MSCT). Therefore, another 6 cycles of second line chemotherapy (paclitaxel/cisplatin) were initiated. On June 2016, blastic lesion on right inferomedial caput femur were found and capecitabine were started on July 2016. On follow-up MSCT done on March 2017, multiple nodules on both thyroid lobes were found, beside metastatic nodules on both lungs and multiple mediastinal lymphadenopathy. Treatment with capecitabine was continued until present time.

During 2017, several abnormalities were found in her laboratory result. She was pancytopenic and her renal function was impaired. Her last laboratory test on June 20th 2017 showed hemoglobin 9.8 g/dL, hematocrit 28.1%, leukocyte count 4.81 x 10$^3$/µL, platelet count 119.000/µL, and the estimated glomerular filtration rate (eGFR) dropped to 42 mL/min/1.73m$^2$.

From the physical examination, we found the patient was fully conscious with normal vital signs. On dermatological examination, we found multiple, skin colored-erythematous-hyperpigmented plaques, irregular in shape, plaque in size, circumscribed-diffused border, with scales and fissures overlying it on both palms and soles as well as lateral aspect of the feet. On both back of her hand, on proximal interphalangeal and metacarpal joints, and bilateral lateral malleolus, we found multiple, erythematous-hyperpigmented plaques, lenticular until nummular in size, circumscribed, discrete, with lichenification, scales, and fissured overlying it.

Patient was diagnosed with hand-foot syndrome due to capecitabine and was treated with vaseline album as emollient and clobetasole propionate 0.05% ointment twice a day on palms and soles.

Our second patient was a 46-years-old woman who was consulted by Hematology and Oncology Division of Internal Medicine Department on December 7th 2017. She was consulted with breast cancer, thyroid cancer, with metastasis to lungs, brain, mediastinum, and respiratory tract, with chief complaint of dry skin on palms and soles. She was complaining of dry and fissured palms and soles since 2 months ago. It is accompanied with itch and pain while walking.

She had history of prior treatment with capecitabine from May 2009 to August 2012 but experienced nothing unpleasant. Capecitabine treatment was stopped and re-initiated on April 2016 due to respiratory tract metastasis. Two months prior to admission, she complained redness on both palms and soles, accompanied with itch and pain on fissured skin. History of contact with irritants were denied. She uses vinyl gloves everytime she wash clothes or dishes. She overcome the complaints by applying moisturizers and low potency topical corticosteroid but no improvement were noted. She bathes twice a day with baby bar soap and regular temperature water. Patient is planned to receive capecitabine for 5 more years.

From the physical examination, we found the patient was fully conscious with normal vital signs. On dermatological examination, we found multiple, erythematous-hyperpigmented plaques, irregular in shape, plaque in size, circumscribed-diffused border, with scales and fissures overlying it on both palms and soles. Her laboratory test on October 23rd 2017 showed hemoglobin 13.7 g/dL, hematocrit 40.4%, leukocyte count 4.04 x 103/µL, platelet count 303.000/µL. Her renal function were normal with the eGFR 88.7 mL/min/1.73m2 and on December 11th

2017 her eGFR increased to 104.2 mL/min/1.73m2. Patient was diagnosed with hand-foot syndrome due to capecitabine and was treated with vaseline album as emollient and mometasone furoate 0.01% ointment once a day on palms and soles.

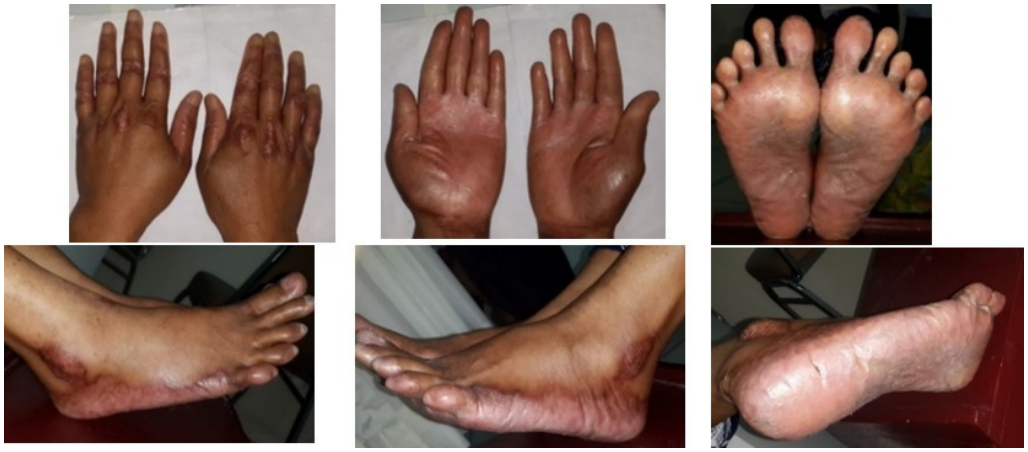

Figure 1. First patient with erythematous-hyperpigmented plaques with scales and fissures on both palms, soles, and lateral aspect of the feet

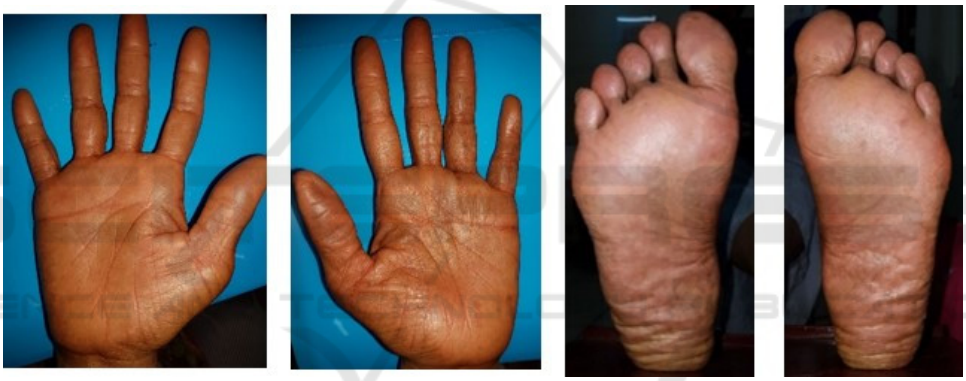

Figure 2. Second patient with erythematous-hyperpigmented plaques on both palms and soles

## 3 DISCUSSION

Various cytotoxic drugs have been reported to have correlation with HFS. 5-fluorouracil (5-FU) has been known to cause HFS since the first description in 1984 (Lokich & Moore, 1984). Occurrence of HFS have been shown to be related to dose and prolonged drug exposure during continuous intravenous infusion, or daily ingestion as in capecitabine which taken by our patients. Our patients were planned to receive long-term maintenance treatment with capecitabine, up to 5 years in our second patient. Gresset reported that the median time of onset is 79 days, ranging from 11 to 360 days (Gressett et al., 2006). In our first patient, the onset is around 1 year prior to admission and in our second patient, HFSoccurred on her second initiation of capecitabine treatment after 3 years of previous cycle, so we can conclude that the onset range of HFS is wide.

The mechanism of HFS remains unclear. However, several theories have been postulated. First, keratinocytes might have upgraded levels of the enzyme thymidine phosphorylase which could lead to capecitabine metabolite accumulation, causing increased possibility of developing HFS. Second, capecitabine may be eliminated by the eccrine glands, which is numerous in palms and soles. Other theory postulates HFS resulting from increased vascularization and increased pressure and temperature in the hands and feet.

From a meta-analysis reported in 1998, HFS induced by 5-FU seems to be more common in elderly female patients (Levy et al., 1998). Interestingly, although our patients suit the gender profile and the fact that capecitabine is a prodrug of 5-FU, the relationship between age or gender and HFS seen with 5-FU has not been clearly seen with capecitabine.

The manifestations of HFS are classified according to their severity by National Cancer Institute (NCI) and World Health Organization (WHO) as shown by Table 1.

Table 1. HFS Grading as defined by NCI and WHO (Webster et al., 2017)

| NCI grade | NCI definition |
|---|---|
| 1 | Skin changes or dermatitis without pain e.g. erythema, peeling |
| 2 | Skin changes with pain, not interfering with function |
| 3 | Skin changes with pain interfering with function |
| **WHO grade** | **WHO definition** |
| 1 | Dysesthesia/paresthesia, tingling in the hands and feet |
| 2 | Discomfort in holding objects and upon walking, painless swelling and erythema |
| 3 | Painful erythema and swelling of palms and soles, periungual erythema and swelling |
| 4 | Desquamation, ulceration, blistering, severe pain |

Both of our patients experienced pain and discomfort in holding objects and upon walking besides skin changes, however no swelling or periungual involvement in both patients, so we classified their HFS as grade 2-3 according to WHO. According to NCI, both patients classified as grade 3. The treatment was tailored based on the clinical manifestations on each patient. The histopathological findings are nonspecific, therefore it was not performed.

HFS is usually self-limiting and rarely leads to life-threatening manifestations. Still, it interferes treatment schedule and patient's quality of life. Thus, proper management is needed to prevent, as well as, to treat HFS. Currently, the mainstay of the management of HFS is interruption of therapy and dose reduction, if necessary. Avoiding potential irritants, including exposure to extreme changes in temperature, ill-fitting shoes, tight-fitting clothing, excessive exercise, and the use of topical anesthetic-containing cream may prevent the development of HFS.

Treatment is focused on supportive therapy to reduce pain and discomfort, also to prevent infections. Simple topical care with wet dressings, topical steroids, and emollients are all that required to clear the condition in some patients. Emollients and creams have been used for prophylactic and symptomatic treatment at first signs of grade 1 HFS. Although the use of steroids for capecitabine-induced HFS is not proven, steroids may acutely reduce inflammation. Moreover, several studies reported that topical or systemic corticosteroids have been useful for prophylaxis and treatment of HFS for a wide variety of different drugs. In our patients, the signs of inflammation were visible, with thickening of the skin. Therefore we gave high to very high potency topical steroids, aiming to reduce the inflammation and relieve symptoms.

In our patients, vaseline album were given. It acts as occlusive agent that coat the stratum corneum to retard transepidermal water loss, as well as provide an emollient effects. In 2-weeks follow up, patients report improvement in symptoms and skin lesions. Pain were reduced and their daily activities are no longer disrupted.

# 4 CONCLUSION

We report 2 cases of HFS due to capecitabine. Both patients were diagnosed based on the history and physical examination and were given topical emollient and steroid. Both patients responded well and reported improvement on skin lesions and quality of life after 2-weeks treatment.

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