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Cutaneous Manifestations of Breast Cancer Patients In Combination With Capecitabine and Lapatinib Chemotherapy

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Abstract: The combination of chemotherapy with lapatinib and capecitabine in human epidermal growth factor receptor 2 (HER2) positive breast cancer is quite effective. The combination of these two agents increases the risk of dermatological toxicities. A woman, 38 years old, HER2 positive breast cancer with a combination of chemotherapy agents between lapatinib and capecitabine gives an overview of skin toxicities such as acneiform eruptions, palmar-plantar erythrodysesthesia (PPE), and paronychia. Therapy, in this case, aims at clinical improvement. The combination of lapatinib and capecitabine has a side effect profile like each drug. Combined use of the two agents increases the incidence of skin side effects, including acneiform eruptions, PPE, and paronychia, compared to monotherapy. Early awareness of the side effects of chemotherapeutic agents is needed for early treatment to prevent the worsening of the condition and discontinuation of chemotherapeutic agents due to drug side effects.

Keywords: acneiform eruption; palmar-plantar erythrodysesthesia; paronychia; lapatinib; capecitabine

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide. According to data from the Global Cancer Observatory of the World Health Organization (WHO), in 2020, there will be 19 million new cancer cases worldwide. Breast cancer ranks first in the increase in new cases, with a total of 2.2 million new cases (11.7%), and ranks fourth for the death rate caused by cancer (6.9%) (WHO, 2020).[1]

Of the total cases of breast cancer, 20-25% of breast cancers have positive human epidermal growth factor receptor 2 (HER2). HER2-positive breast cancer patients have a higher risk of disease progression and death due to the more aggressive nature of the cancer cells and resistance to standard chemotherapeutic agents. Therefore, adequate therapy with chemotherapeutic agents is needed, one of which is a combination of lapatinib and capecitabine.[2,3] The combination of lapatinib and capecitabine has been approved by the Food and Drug Administration (FDA) to treat HER2-positive patients who have received previous treatment, including anthracyclines, taxane, and trastuzumab.[4]

Side effects of lapatinib that have been reported on the skin include papulopustular rash (acneiform), pruritus, xerosis, fissures, alopecia, hypertrichosis, mucositis, [5,6] Side effects of capecitabine on the skin include palmar-plantar erythrodysesthesia (PPE), hyperpigmentation, nail changes, alopecia and stomatitis. [7] Side effects can range from mild to severe and may require dose adjustment or discontinuation of therapy.[8]

This paper reports 1 case of a patient with acneiform eruptions, PPE, and paronychia in HER 2 positive breast cancer patients with the combination of lapatinib and capecitabine chemotherapy agents. This case report aims to increase the clinician's knowledge about the diagnosis and side effects on the skin due to the combination of chemotherapy agents; lapatinib and capecitabine.

CASES

A 38-year-old woman who was a housewife came to the Dermatology Venereology center of Dr. Sardjito Hospital Yogyakarta with complaints of papules on the face and pain around the fingernails of both hands and feet. Since five months ago, the patient has complained of sores and frequent bleeding on the edges of the fingernails and toes that were painful, accompanied by black spots on the palms and feet that were not painful. The patient used the soft u derm® cream, and after one month, the complaints felt better. The black spots on the palms faded and became red. Seven days ago, the patient complained of a little itchy rash on the face, which increased in number and spread to the scalp. The patient had not consulted and tried to treat the complaint. On the day of the examination, sores and bleeding on the edges of the painful nails were still there; red spots on the palms of the hands, black spots on the soles of the feet, and pimples on the face persisted. Complaints of diarrhea, nausea, vomiting, pain in both palms and feet, canker sores, and hair loss were denied. The patient could still carry out daily activities as usual.

The patient was diagnosed with stage 3 breast cancer with positive human epidermal growth factor receptor type 2 (HER 2) 21 months ago. She underwent a breast mastectomy 20 months ago and completed six cycles of chemotherapy with doxorubicin, cyclophosphamide, and docetaxel regimens 13 months ago. Therapy was followed by radiotherapy 25 times with a total dose of 50Gy, completed ten months ago. Six months ago, the patient started receiving adjuvant chemotherapy agents, namely a combination of capecitabine (1500 mg-0-1000mg) and lapatinib (1x 1250 mg) which is still routinely consumed today. The patient denied the use of drugs other than chemotherapy.

Similar complaints were previously denied. The patient had no history of diabetes mellitus, hypertension, allergies, or atopy, and also contactan, such as Lifebouy® for bath and face soap and Pantene® shampoo for shampooing. The patient used soft u derm® moisturizer for the palms of the hands, feet, and nails. She never washed his clothes and denied using cosmetic products or facial treatments before and after chemotherapy. Similar complaints were also denied by the patient's family.

On physical examination, the patient was composted mentis with the impression of adequate nutrition. Vital signs were within normal limits, and no enlarged lymph nodes were found. Dermatological status on almost the entire face showed the presence of multiple monomorphous skin-colored papules with pustules. On the plantar, there were macules and multiple irregularly sized hyperpigmented patches of varying size scattered with hyperkeratosis in the right I metacarpal area. There were macules on the palms and soles and multiple scattered, indistinct erythematous and hyperpigmentation patches of varying size. In the periungual digits II, III, and digits I, II, and V of the right and left limbs, and the right and left third digits of the right and left, the digit manus I Sinistra appeared erosions and erythematous. On digit I pedis dextra, onychodystrophy was seen. The condition of the nails of both hands and other toenails was within normal limits. The patient's skin was xerotic.

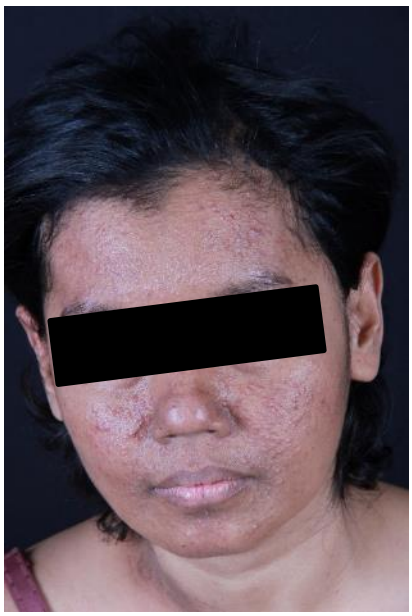
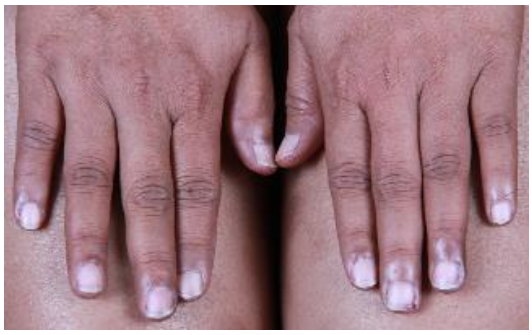
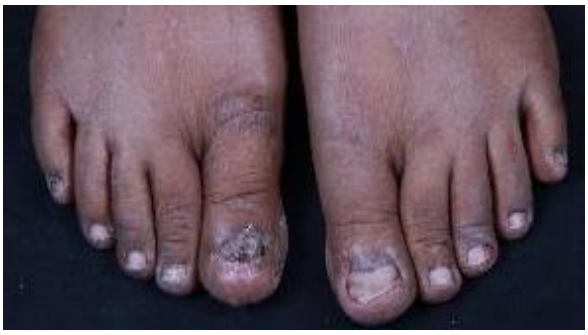


Figure 1. Photograph showing the presence of multiple monomorphous skin-colored papules with pustules



(1)

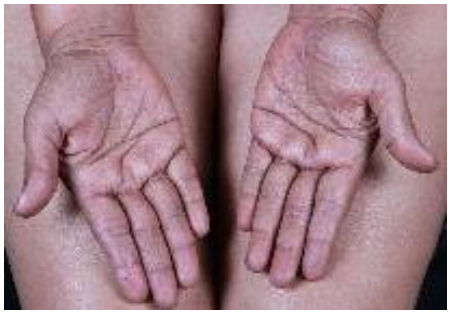


(2)

Figure 2 and 3. Erosions and erythematous appear in the periungual of multiple digits of both hands and feet. On digit I pedis dextra, onychodystrophy was seen.

The differential diagnosis for facial lesions was acneiform eruption due to a combination of lapatinib capecitabine, demodicosis, and pityrosporum folliculitis. The differential diagnosis for lesions on the palms and soles was PPE and palmoplantar keratoderma. The differential diagnosis of nail margin lesions was paronychia due to a combination of lapatinib capecitabine, paronychia due to infection, and allergic contact dermatitis. Woods lamp examination of the face did not reveal a bluish-white fluorescence with a follicular pattern. The KOH examination on the face did not reveal Malassezia sp or Demodex sp. On examination of the nail of edge lesions with Gram preparations, there were polymorphonuclear cells without any bacteria found. KOH examination on the nail did not reveal any yeast or fungus, and we did not do a nail culture examination due to cost problems. Based on the history of physical examination and supporting examination, the patient's diagnosis was an acneiform eruption, PPE, and paronychia due to the combination of lapatinib and capecitabine.

The patient received clindamycin gel 1% twice daily for the face. For nail edge lesions, palms and soles, she obtained 10% Betadine Spotted and Soft U Derm® moisturizer twice a day. Patients were also educated to replace their soap with moisturizing liquid bath soap. A combination of chemotherapy in the patient was continued by observing the skin lesions.



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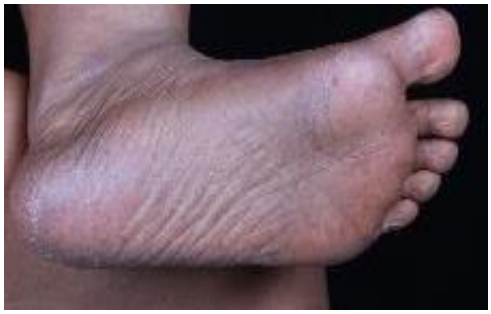

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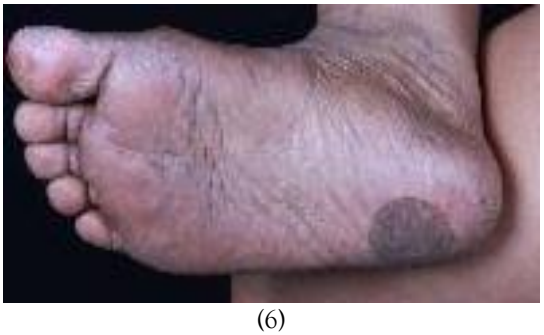

(6)

Figure 4,5,6. There are macules on the palms and soles and multiple scattered, indistinct erythematous and hyperpigmentation patches of varying size.

DISCUSSION

Establishing the diagnosis in the form of acneiform eruptions, PPE, and paronychia due to the combination of lapatinib and capecitabine, in this case, was based on the history, physical examination, and laboratory. Lapatinib is a small-molecule inhibitor of the tyrosine kinase domain of EGFR and HER2. Capecitabine is a chemotherapeutic agent that is converted to fluorouracil by thymidine phosphorylase in the human body and is one of the agents commonly used in breast and colorectal cancer.[9,10]

The combination of lapatinib and capecitabine is adjuvant chemotherapy approved for treating patients with HER2-positive breast cancer in advanced stages or with metastases. The side effect profile of the combination therapy of lapatinib and capecitabine is similar to that of each drug. There were no relevant pharmacokinetic interactions at the recommended combination therapy doses, namely lapatinib at a dose of 1250 mg daily and capecitabine at a dose of 2000 mg daily.[10]

Lesions on the patient's face were differentially diagnosed with acneiform eruptions due to the combination of lapatinib and capecitabine, demodicosis, and pityrosporum folliculitis. Acneiform eruptions are characterized by erythematous papules and pustules of monomorphic form that develop on the face, scalp, and upper body. The acneiform eruption is a side effect often reported with lapatinib in 40%-90% of patients. The lapatinib-associated acneiform eruption appears clinically different from other single-target EGFR agents in that the rash tends to be more localized. [11,12]

The mechanism of rash caused by the use of lapatinib is related to the expression of HER, a member of the EGFR family in the dermis and epidermis. Inhibition of EGFR can prevent keratinocyte migration and keratinocyte apoptosis.[13] In addition, modulation of cytokine release caused by EGFR blockade in keratinocytes causes the entry of inflammatory cells into the dermis and epidermis, resulting in a prototype acneiform rash dominated by inflammation. [14] On the use of capecitabine agents, side effects of acneiform eruptions are very rare. There is only one case report by Kara et al., who reported a case of acneiform eruption in a patient with small cell neuroendocrine carcinoma receiving capecitabine.[15]

Demodex folliculorum and Demodex brevis are obligate parasites in sebaceous glands and hair follicles. When the immune system is suppressed, as in cancer patients undergoing chemotherapy, it becomes susceptible to obligate parasites such as D. folliculorum and D. brevis.[16] Pityrosporum folliculitis is an infection of the hair follicles caused by Malassezia furfur (Pityrosporum ovale) and other strains of Malassezia. Malassezia is a dimorphic lipophilic yeast found in small amounts in the stratum corneum and hair follicles of up to 90% of healthy individuals. Papulopustular folliculitis is most commonly found on the chest, back, and upper arms and less often on the face, often misdiagnosed as acne.[17] In cancer patients undergoing chemotherapy, the immune system becomes suppressed, making them susceptible to infestation of this parasite. Parasite infestation is also frequently associated with steroid-induced dermatitis.[18] In the patient, a history of using face creams was also denied. On examination of scrapings with KOH, no Demodex sp or spores and yeast from Malassezia were found. On examination with a Woods lamp, no bluish-white fluorescence was found with a follicular pattern. In this case, the presence of monomorphic papules, a history of chemotherapy treatment with lapatinib capecitabine, and the above investigations confirmed the diagnosis by acneiform eruptions due to the combination of lapatinib capecitabine.

The differential diagnosis of nail lesions is paronychia due to a combination of chemotherapy agents, paronychia due to infection, and contact dermatitis. Paronychia is inflammation of the soft tissue around the nail (periungual). The clinical manifestations of paronychia are edema, erythema, pain, and granulation tissue formation around the fingernail and toenail folds. In some conditions, bleeding or exudation may occur, resulting in incrusting. [19] Paronychia includes acute (6 weeks duration) and chronic (> 6 weeks duration), and there is usually damage to the barrier between the nail plate and the adjacent nail fold. Paronychia is often caused by bacterial or fungal pathogens, especially Candida albicans. Other etiologies include exposure to chemical irritants, moisture, systemic conditions, and drugs.[20]

Paronychia induced by chemotherapy agents is a sterile inflammation of the nail fold. Anti-EGFR chemotherapy agents, including lapatinib, have been associated with the development of chronic paronychia. The onset of paronychia induced by EGFR chemotherapy agents can occur as early as 4-8 weeks of therapy but can also occur six months after therapy is initiated. The incidence of paronychia in patients receiving EGFR chemotherapy is highest in the Asian population, 45.8%. [20,21] In clinical trials, adverse events of capecitabine as monotherapy in nails have rarely been reported. The etiology of nail changes due to chemotherapy remains unclear. Immunosuppression may be possible due to chemotherapy's direct effects on the nail, especially on the nail matrix and soft tissue around the nail. Bacteria and fungi can be eliminated. There was also no history of contactants in the patient, so both differential diagnoses were ruled out, and the patient was diagnosed with paronychia due to the combination chemotherapy of lapatinib and

capecitabine. The differential diagnosis proposed for palmar-plantar lesions is PPE and palmoplantar keratoderma. Palmar plantar erythrodysesthesia (PPE) or hand-foot syndrome is a skin disorder in the form of erythematous patches on the palms of the hands and feet, accompanied by pain and desquamation which is often caused by cytotoxic agents such as 5-fluorouracil (5-FU), pegylated liposomal doxorubicin (PLD), docetaxel, capecitabin, sorafenib, and gefitinib. The pathophysiology of PPE relates to the pharmacokinetics and pharmacodynamics of chemotherapy drugs and the skin structure of the palms and soles. Eliminating the drug through the eccrine glands causes the drug to accumulate in the palms of the hands and feet, which have many eccrine glands. Metabolites that accumulate in the skin of the palms and soles will damage keratinocytes directly or affect the proliferation of keratinocytes in the stratum basale.[24] Palmoplantar keratoderma usually appears as a paraneoplastic phenomenon that occurs with cancer. [25] In this case, the complaint occurred after the patient underwent a combination of chemotherapy with lapatinib and capecitabine for one month so that palmoplantar keratoderma could be ruled out. Changes in the color of the patient's palms and feet to blackish without pain, accompanied by a history of chemotherapy, led to the diagnosis of PPE.

Although side effects were found in the form of acneiform eruptions, PPE, and paronychia, acneiform eruptions and paronychia side effects were more frequently reported with the use of lapatinib agents. In contrast, PPE side effects were more common with the cape. Several studies have reported a higher incidence of side effects with the combined use of lapatinib and capecitabine than with monotherapy. Early detection of side effects of chemotherapy drugs can provide a better prognosis and reduce the degree of toxicity of side effects. The scoring system commonly used to assess the degree of toxicity from acneiform eruptions, PPE, or paronychia is the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0 version 2010. Scores were assessed based on the patient's clinical and subjective symptoms, such as pain and disturbances in activity.

The scoring system for paronychia uses NCI-CTCAE with grade 1 in the form of edema or erythema in the nail fold and cuticle damage; grade 2 in the form of edema or erythema accompanied by pain .[20] Topical povidone-iodine 2% in dimethylsulfoxide is considered very effective in reducing signs and symptoms of chemotherapy-associated paronychia. [22] In this case, the patient experienced acneiform eruption grade 1, PPE grade 1, and paronychia grade 2. The side effects that occurred in the patient could still be tolerated, so chemotherapy drugs were continued by considering the risks and benefits to the patient. The patient was given topical antibiotics, spotted povidone-iodine, moisturizer, and education for soap replacement.

CONCLUSION

We reported one case of an acneiform eruption, PPE, and paronychia caused by the combination of chemotherapy agents between lapatinib and capecitabine. The diagnosis was based on history, physical examination, and laboratory findings. For each side effect on the skin due to chemotherapy, it is necessary to assess the degree of severity as it is related to management. The administration of therapy, in this case, was to prevent the worsening of side effects so as not to interfere with the patient's chemotherapy.

CONFLICT OF INTEREST

No conflict of interest.

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