Lenalidomide-induced hand-foot syndrome: A case report

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ABSTRACT:

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Hand-foot syndrome (HFS, palmoplantar erythrodysesthesia, chemotherapy-induced acral erythema) is a reaction which occurs after administration of systemic medications especially chemotherapeutic drugs. The usual clinical presentations include erythema, edema and a burning pain on the palms and soles. To the best of our knowledge, hand-foot syndrome caused by lenalidomide has never been reported.

We reported a case of a 57 year-old Thai woman with multiple painful edematous papules on her palms and soles after receiving lenalidomide in the treatment of relapsed and refractory multiple myeloma. The clinical and histopathologic findings are compatible with hand-foot syndrome. She was diagnosed with lenalidomide-induced hand-foot syndrome and treated with topical steroid and dose reduction of lenalidomide. The resolution of disease was observed at a 3-week follow-up visit.

Key words: Hand-foot syndrome, palmoplantar erythrodysesthesia, chemotherapy-induced acral erythema, lenalidomide

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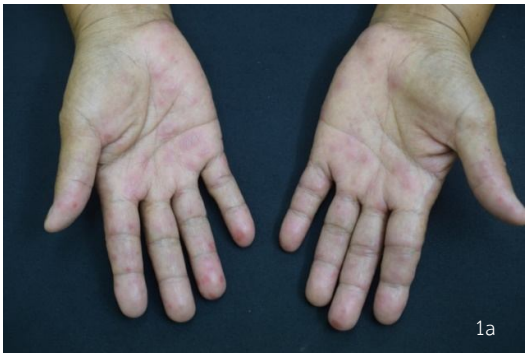
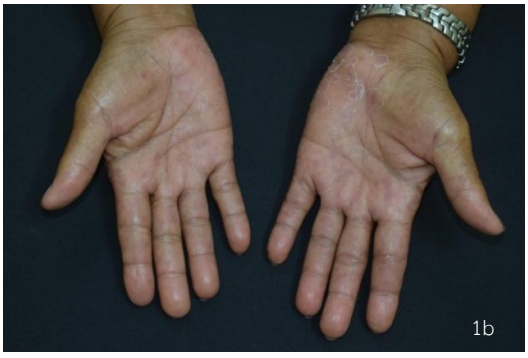
Introduction

Hand-foot syndrome (HFS) is also known as palmoplantar erythrodysesthesia or chemotherapy-induced acral erythema. HFS is a reaction which occurs after the administration of cytotoxic chemotherapies characterized by painful erythema and edema of palms and soles[1].

Lenalidomide, a thalidomide analogue, is an immunomodulatory drugs used primarily in the treatment of multiple myeloma, myelodysplastic syndrome and amyloidosis[2]. This report demonstrated the first case of lenalidomide-induced hand-foot syndrome.





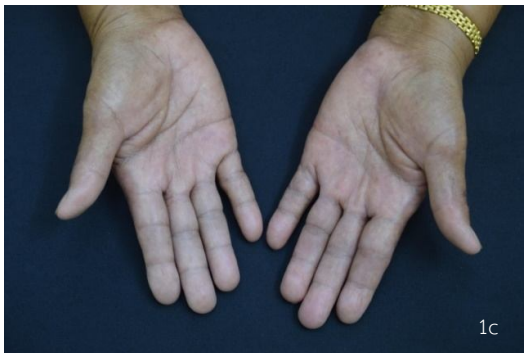


Figure 1 Multiple ill-defined erythematous edematous papules and plaques on both palms and soles (a). Improvement after treatment with dose reduction of lenalidomide and topical steroid for 1 week (b). Resolution after treatment with dose reduction of lenalidomide and topical steroid for 3 weeks (c).

Our case

A 57-year-old Thai woman presenting with anemia was diagnosed with multiple myeloma for five years. She had been treated with multiple chemotherapeutic regimens since 2014. However, she still had relapses of disease and diagnosed with relapsed and refractory multiple myeloma. Recently, she received a chemotherapeutic regimen including lenalidomide, daratumumab, and dexamethasone for five cycles from May to September 2018 followed by autologous hematopoietic stem cell transplantation in October 2018. The bone marrow biopsy on January 2019 showed no residual atypical plasma cell. She had chemotherapy-free interval

from October 2018 to January 2019. Later on, the hematologist started lenalidomide at the dose of 25 milligram once-daily on February 2019 as part of the maintenance therapy. The patient did not receive any other chemotherapeutic agents, except for lenalidomide at that time. Two weeks later, she developed a painful rash on her palms and soles. Physical examination revealed multiple ill-defined erythematous edematous papules and plaques on both palms and soles (Figure 1a).

The skin biopsy was performed on her left palm. Histopathology is consistent with toxic erythema of chemotherapy. There were sheets of necrotic keratinocytes in the upper epidermis, slightly interface vaculolar change at dermo-epidermal junction, spongiotic epidermis and sparse superficial perivascular infiltration with lymphocytes (Figure 2). No eccrine gland necrosis was observed. As a result, she was diagnosed with lenalidomide-induced hand-foot syndrome.

Discussion

Hand-foot syndrome was reported for the first time in 1974 by Zuehlke RL[3]. The characteristic feature is painful erythematous lesions on palms and soles so it can be called palmoplantar erythrodysesthesia or chemotherapy-induced acral erythema[1,4].

Hand-foot syndrome often appears in first few weeks after administration of the chemotherapeutic drug. The common causative drugs are anthracyclines (e.g. doxorubicin, pegylated liposome-encapsulated doxorubicin), taxanes (e.g. docetaxel) and pyrimidine analoques (e.g. cytarabine, 5-FU)[4,5].

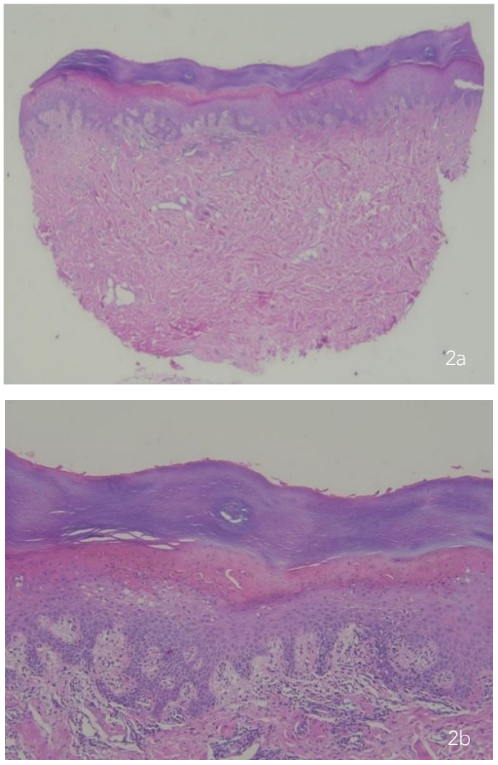


Figure 2a,2b The sections demonstrate sheets of necrotic keratinocytes in the upper epidermis, slightly interface vaculolar change at dermo-epidermal junction, spongiotic epidermis and sparse superficial perivascular infiltration with lymphocytes. (a) H&E, X20, (b) H&E, X100

The initial manifestation is dysesthesia on plamoplantar sites, followed by painful

edematous erythematous rash that could lead to blistering, desquamation, andsubsequent erosion or ulceration. The common sites are palms and soles but it can appear on dorsal part of hands and feet or intertriginous area in more severe cases.

The pathogenesis of HFS is not fully understood. It was hypothesized to be a toxic response caused by local accumulation of the drug resulting in the degeneration and necrosis of the sweat glands[6,7].

The severity of HFS is graded by different classifications. Three and four degrees of severity were graded by National Cancer Institute classification and World Health Organization respectively following to severity of clinical manifestations and histopathological findings[4].

The histopathology of mild grade disease shows dilated capillaries. Interface dermatitis with varying degrees of necrotic keratinocytes, dilated capillaries and dermal edema are seen in more severe form. There is usually only mild perivascular lymphohistiocytic infiltration. Eccrine squamous syringometaplasia can also be seen in severe disease[1,4].

Lenalidomide is the immunomodulatory drug used mainly in the treatment of multiple myeloma, myelodysplastic syndrome and amyloidosis. This drug has not only immunomodulatory effect, but also antitumor and anti-angiogenic effect. Possible adverse effects of lenalidomide are myelosuppression, fatique, dizziness, peripheral neuropathy, constipation, venous thrombosis and skin eruption[8]. A retrospective study reported the incidence of cutaneous adverse effects of lenalidomide ranged from 12% to 43% which demonstrated as maculopapular, dermatitic, acneiform, urticarial or undefined eruption[2,8]. To our knowledge, there has been no previously published data of hand-foot syndrome as the cutaneous adverse effect of lenalidomide.

Nowadays, there is no standard treatment of HFS. The suggestive managements are from case reports and expert recommendations. Dose reduction or discontinuation of the causative drugs often lead to rapid improvement within weeks. Increasing the interval between cycles is another suggestive management. Various topical modalities such as topical analgesia, steroid, emollient and cold compression were reported to be effective in symptoms relief[9].

Our patient was diagnosed with lenalidomide-induced hand-foot syndrome because she did not receive any other chemotherapeutic agents, except for lenalidomide at that time. She was treated with dose reduction of lenalidomide from 25 to 5 milligram once-daily along with potent topical steroid. We found that the skin lesion was markedly improved on a 1-week follow-up

(Figure 1b). After three weeks of treatment, all the skin lesions disappeared (Figure 1c).

We hypothesize that the reason why the patient did not develop HFS when she received lenalidomide last year is because she concomitantly received oral dexamethasone which has been described in retrospective analyses as effective treatment for improvement of HFS lesion caused by pegylated liposome-encapsulated doxorubicin[10]. This systemic corticosteroid may have suppressed the inflammation and masked the clinical manifestation of our patient. Nonetheless, the result of the systemic steroid use to prevent or treat hand-foot syndrome still has insufficient data, and the risk-to-benefit ratio has yet to be determined.

In conclusion, we reported the first case of lenalidomide-induced hand-foot syndrome with a resolution after being treated with topical steroid and dose reduction of lenalidomide for 3 weeks.

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