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Case Report

Ribociclib-Induced Erythema Dyschromicum Perstans (Ashy Dermatosis)–Like Pigmentation in a Metastatic Breast Cancer Patient

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Conflicts of Interest
The authors declare that they have no competing interests.

ABSTRACT

Ribociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that has been approved in combination with endocrine therapy for the treatment of hormone receptor-positive/human epidermal growth factor 2-negative advanced or metastatic breast cancer. The main dermatological adverse events associated with CDK 4/6 inhibitors that are described in the literature include skin rash, an increased risk of alopecia, and stomatitis. Erythema dyschromicum perstans (EDP), also known as ashy dermatosis, is characterized by acquired small and large slate-gray hyperpigmented macules with erythematous borders. There are currently no published reports of EDP-like or pigmentary changes induced by CDK 4/6 inhibitors. This report describes the first case of EDP-like pigmentation associated with ribociclib therapy.

Keywords: Ashy dermatosis; Breast; Erythema dyschromicum perstans; Ribociclib

INTRODUCTION

Ribociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that has been approved in combination with endocrine-based therapy for the treatment of women with hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2−) advanced or metastatic breast cancer [1].

CDK 4/6 inhibitors represent an emerging group of targeted anticancer therapies. The cyclin D-CDK 4/6 pathway controls the G1 (pre-DNA synthesis) to S (DNA synthesis) transition, and its activation in cancer leads to abnormal cell proliferation. The common toxicities associated with CDK 4/6 inhibitors include hematological adverse events such as neutropenia, leukopenia, and anemia; and non-hematological toxicities such as fatigue, impaired liver function, prolonged QTc interval, nausea, and diarrhea [2].

The main dermatological adverse events associated with CDK 4/6 inhibitors that have been described in the literature include skin rash, an increased risk of alopecia, and stomatitis [3-7].

Author Contributions

Conceptualization: Mariano M, Donati P, Cameli N, Morrone A, Cristaudo A; Data curation: Mariano M, Cameli N, Morrone A; Investigation: Mariano M, Cristaudo A; Methodology: Mariano M, Donati P, Pigliacelli F, Cristaudo A; Resources: Mariano M, Donati P; Supervision: Mariano M, Cameli N, Morrone A, Cristaudo A; Validation: Mariano M, Cameli N, Pigliacelli F, Morrone A, Cristaudo A; Visualization: Mariano M, Donati P, Cameli N, Morrone A, Cristaudo A; Writing – original draft: Mariano M, Donati P, Cameli N; Writing – review & editing: Mariano M, Donati P, Pigliacelli F, Morrone A, Cristaudo A.

There are currently no published reports of erythema dyschromicum perstans (EDP)-like pigmentary changes induced by CDK 4/6 inhibitors.

This report describes the presentation of an unusual case of EDP or ashy dermatosis (AD)-like pigmentation associated with ribociclib therapy.

CASE REPORT

A 37-year-old woman (Fitzpatrick skin type IV) who had HR+/HER2− metastatic breast cancer (metastasis to the axillary and retropectoral lymph nodes, and bone metastasis to sternum) visited our clinic in January 2020 because of a slate-gray hyperpigmentation of the photoexposed skin. Ten months before this visit, she had undergone bilateral radical mastectomy with monolateral lymphadenectomy, and prophylactic oophorectomy. Two weeks (March 2019) after the surgical procedures, she was started on endocrine therapy with letrozole.

The CDK 4/6 selective inhibitor ribociclib was added to her treatment regimen in June 2019. Two months later, in August 2019, she started to develop an itchy, brown, macular rash that initially appeared on the upper and lower extremities and then spread to all the photoexposed areas of the face, neck, neckline, arms, and legs. The patient reported an evolution of the clinical picture with progressive darkening of the skin to a gray-blue color, dryness, defective skin healing, and pruritus.

Physical examination showed symmetric, ill-defined, brown and slate-gray, hyperpigmented, reticulated, large (>5 cm) macules and patches with erythematous borders that were distributed on the forehead, cheeks, neck, neckline, arms, and legs, sometimes becoming confluent and covering extensive areas (**Figures 1** and **2**). The trunk was spared. Mild xerosis and desquamation were detected. Because of the clinical suspicion of an EDP-like pigmentation, a punch biopsy was performed. The histological examination showed

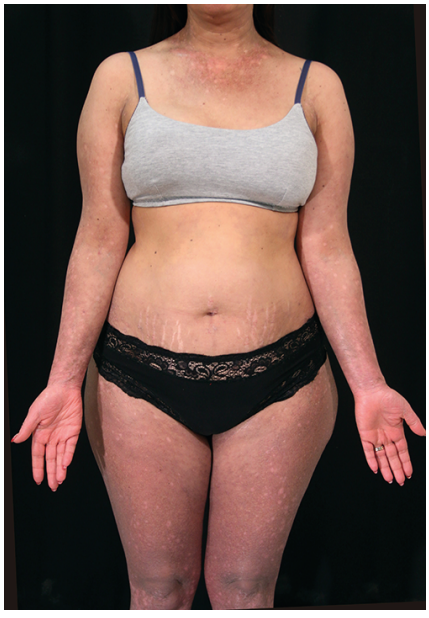

Figure 1. Slate-gray symmetric hyperpigmentation of the photoexposed skin.

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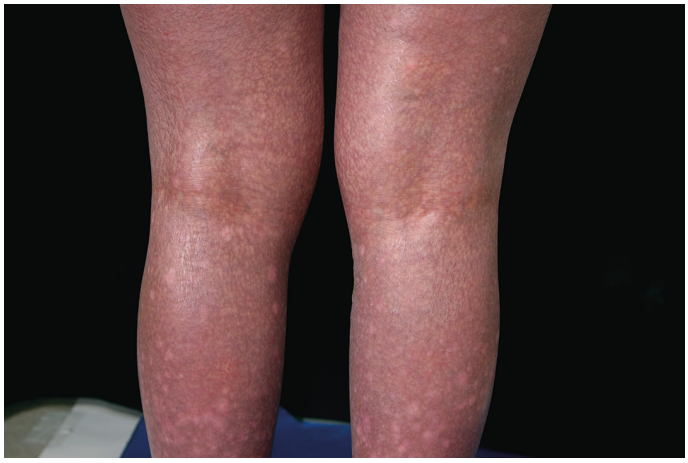

Figure 2. Multiple, slate-gray, hyperpigmented, reticulated macules and patches with erythematous borders on both legs.

moderate inflammatory infiltrate at the dermo-epidermal junction, and pigmentary incontinence and melanophages in the upper dermis (**Figure 3**).

Based on the clinicopathologic diagnosis of ribociclib-induced EDP-like pigmentation, and the great discomfort reported by the patient because of the itching and sensitive skin, ribociclib administration was discontinued; however, letrozole treatment continued unchanged.

The patient was prescribed a course of oral prednisone (25 mg/day), an oral antihistamine, and a topical emollient. At the follow up visit, within a month of discontinuing ribociclib, her cutaneous manifestations appeared to have improved and the hyperpigmentation had started to clear.

The principles of the Declaration of Helsinki as revised in 2013 were followed. Signed informed consent has been obtained from the patient granting approval for the publication of identifying material, including photographs.

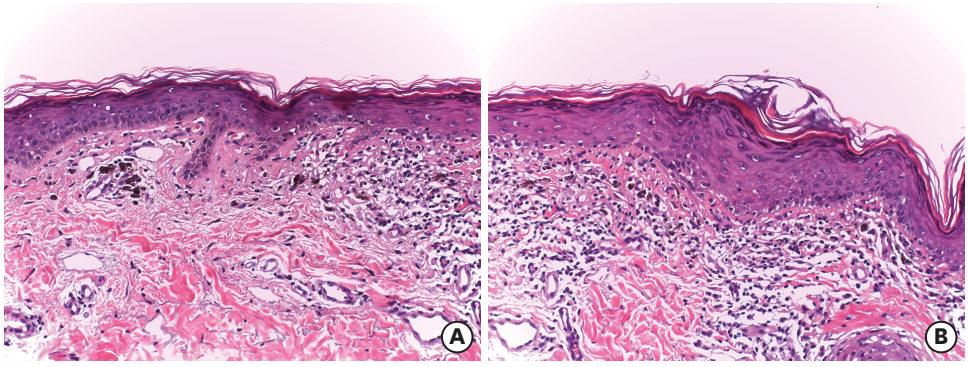

Figure 3. Hematoxylin and eosin staining showing interface lichenoid dermatitis and abundant pigment incontinence in the upper dermis. (A) magnification, ×100 (B) magnification, ×200.

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DISCUSSION

Skin toxicities associated with CDK 4/6 inhibitors have not been commonly reported in the literature. Skin rash, alopecia, and stomatitis have been reported as ribociclib-related adverse events [3].

Cutaneous and gastrointestinal leukocytoclastic vasculitis, subacute cutaneous lupus erythematosus, Stevens–Johnson syndrome, and toxic epidermal necrolysis induced by the CDK 4/6 inhibitor palbociclib have also been described [4-6]. Enhanced dermatologic toxicity has been reported following concurrent treatment with palbociclib and radiation therapy [7]. Pigmentary changes induced by CDK 4/6 inhibitors have not been reported in the literature.

The clinical picture observed in our patient, consisting of slate-gray hyperpigmented macules, both clinically and histologically resembled those of EDP, also known as AD because of the ashy blue-gray color of the lesions.

Initially described as AD by Ramirez in El Salvador in 1957, EDP is an acquired hyperpigmentation disorder with a higher prevalence in Asian and Latin populations and in dark skin phototypes (Fitzpatrick skin types III–VI). The term "erythema dyschromicum perstans" was introduced by Convit in 1961 because of the erythematous borders of the evolving lesions. The term "ashy skin" has a negative connotation for dark-skinned ethnic groups; therefore, EDP was preferred as the term to be used rather than AD [8].

The histological features of EDP can seem similar to other inflammatory disorders including lichenoid reactions [8]. The etiology of EDP is unclear and the underlying causes remain mostly unknown [8]. EDP has been associated with intestinal parasitism, hepatitis C infections, and human immunodeficiency virus seroconversion [8]. When a specific agent is identified as the underlying cause, the condition should be referred to as AD- or EDP-like pigmentation secondary to the specific etiology [9].

Pigmentation that is identical to the morphology of EDP/AD has been reported to occur due to drugs such as proton pump inhibitors, ethambutol, fluoxetine, and chlorothalonil [8]. AD-like hyperpigmentation that developed 6 months after starting treatment with the drug, has been recently described as being associated with the epidermal growth factor receptor inhibitor osimertinib [10].

The underlying pathogenetic mechanism for drug-induced EDP is still not fully known, similar to the idiopathic form of EDP.

Our patient experienced pigmentary changes 2 months after starting ribociclib treatment. This is compatible with the reported latency period for drug-induced EDP/AD [10]. Letrozole-induced EDP/AD was excluded because the cutaneous manifestations started to clear after ribociclib was discontinued and also because skin-related adverse events associated with aromatase inhibitors are uncommon.

In our case, the histopathological examination showed an interface lichenoid dermatitis and abundant pigment incontinence in the upper dermis that was distributed on the interstices and surrounding capillaries (**Figure 3**), as has been reported in the literature in patients with EDP/AD.

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Different therapies (isotretinoin, topical tacrolimus, dapsone, narrow band ultraviolet B therapy) have been used with little benefit and no gold standard therapy is available for the treatment of EDP [8]. Our patient was first given oral prednisone and a topical emollient to alleviate inflammation. It was then decided that she would continue with the application of emollients only.

To our knowledge, this is the first reported case of EDP (AD)-like hyperpigmentation induced by a CDK 4/6 inhibitor.

The CDK 4/6 inhibitors are a new, emerging class of targeted anticancer therapies. Therefore, it is important to recognize and manage new possible cutaneous toxicities associated with their use, in order to improve supportive care in oncological patients.

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