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Vitiligo-Like Depigmentation as a Rare Adverse Effect of Ribociclib in Metastatic Breast Cancer

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Introduction

Cyclin Dependent Kinases 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, abemaciclib are currently approved by U.S. Food and Drug Administration (FDA) for treatment of Hormone Receptor positive (HR–Positive) and Human Epidermal growth factor Receptor-2-negative (HER2-negative) metastatic breast cancer [1]. The combination of CDK4/6 inhibitors and endocrine therapy significantly improved the outcomes of patients with HR–Positive and HER2-negative metastatic breast cancer [2]. Updated results of pivotal trials showed significant improvement in overall survival (OS) of ribociclib plus endocrine therapy with respect to endocrine therapy alone with median OS of 58.7 months with ribociclib vs 41.5 months with placebo plus fulvestrant [3]. Common side effects of CDK4/6 inhibitors include nausea, anemia, cytopenias, fatigue, diarrhoea, and elevated liver enzymes [4]. Recent data suggests a significant increase in number of cases of depigmentation secondary to CDK4/6 inhibitors [5-7].

Case Presentation

A 77-year postmenopausal lady with hypertension, was diagnosed with carcinoma of the left breast with de-novo lung and skeletal metastases. She was found to have a hormone positive, HER2 negative (with an Allred score of ER7/PR 3) metastatic breast cancer. Patient received treatment with CDK 4/6 inhibitor (Ribociclib) with an Aromatase inhibitor (Letrozole) for 15 months.

Subsequently, as shown in Figure 1 and 2, patient developed hypopigmented patches over bilateral lower extremities over a period of 8 months, which were brought to her notice as the intensity of hypopigmentation worsened. The number of lesions and intensity of hypopigmentation increased progressively. She did not have any history of pigmentation disorders in her family. Histopathological examination of depigmented macules showed loss of basal melanocytes. Patient was started on topical emollients and topical steroids and treatment with ribociclib was continued. As of last follow up , patient's disease status is stable.

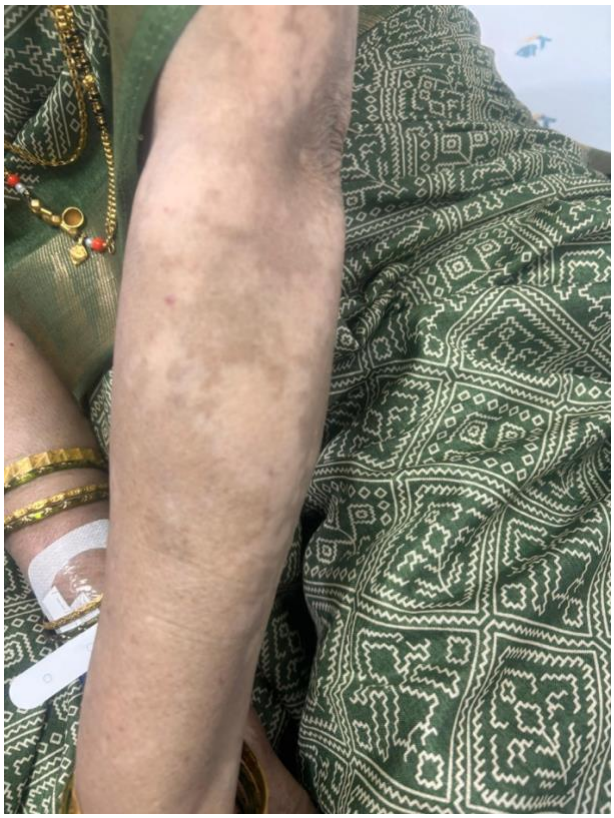

Figure 1

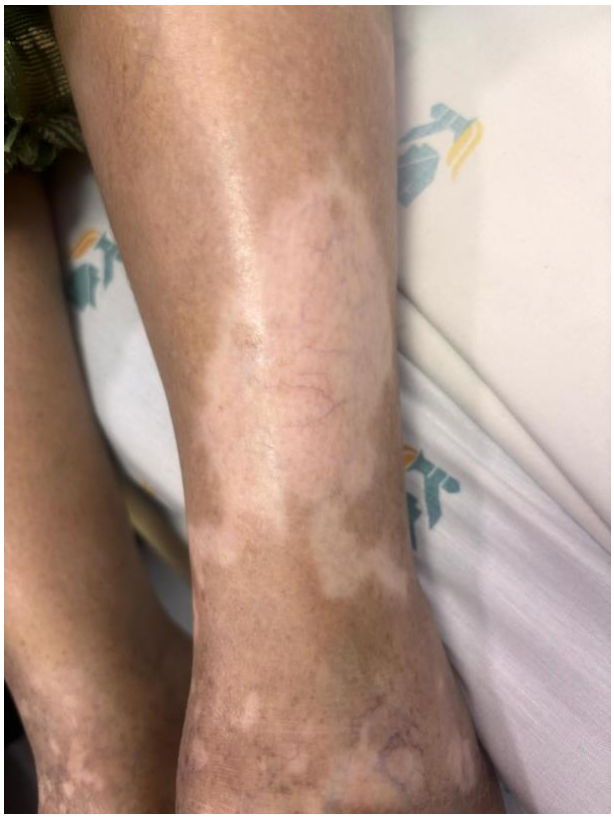

Figure 2

Discussion

Though vitiligo-like lesions are rare with CDK4/6 inhibitors, there is increasing, yet, under reported incidence of development of treatment related depigmented lesions.

Vitiligo is an autoimmune disorder, manifested as hypopigmented macules secondary to loss of melanocytes. Common skin manifestations with CDK4/6 inhibitors are stomatitis, xerosis, alopecia, skin rash, pruritus, severe immune mediated drug reactions like Stevens Johnson syndrome, Toxic Epidermal Necrolysis and rarely vitiligo like lesions.

Rashes were usually reported in the first month while alopecia and nail alterations presented in the second and third months of initiating the medication. The pathogenesis of vitiligo like lesions with CDK4/6 inhibitors is poorly understood.

Proposed hypotheses include:

• Dysregulation of keratinocytes resulting in loss of survival stimulus to the (neighbouring melanocytes [12].

• Apoptosis and altered proliferation of melanocytes and keratinocyte precursors secondary to CDK4/6 inhibitors [12].

Anders et al. (2020) emphasized the significance of targeted therapies in breast oncology, noting that while CDK4/6 inhibitors are effective for HR+/HER2- breast cancer, they may cause adverse effects affecting multiple systems, including dermatological events as observed in this case. This underscores the importance of a multidisciplinary approach, integrating oncologists and dermatologists to balance treatment efficacy with quality of life [8].

Morikawa et al. (2016) suggested that vitiligo development in patients receiving immune checkpoint inhibitors may be linked to better survival, although this remains an unconfirmed observation [9].

Sollena et al. (2023) [10], concluded that most dermatological adverse events occur in breast cancer patients treated with any of the CDK4/6 inhibitors. In majority of the patients, continuing treatment despite cutaneous reactions is recommended, but it remains a therapeutic challenge. Other European studies highlighted that vitiligo-like skin lesions may appear at the later stages (6-8 months) of ribociclib treatment. The use of medium-to-high-potency topical corticosteroids should be considered as the treatment of choice.

Additionally, Bang et al. (2024) [11] conducted a multicentre retrospective study reviewing the vitiligo-like lesions in breast cancer patients treated with CDK4/6 inhibitors. They analysed 10 cases from academic centres in the United States and Europe, describing the clinical characteristics, progression, and management. The study highlighted the persistence of the lesions despite treatments and investigated ruxolitinib as a potential treatment option.

The latency of vitiligo-like lesions from the initiation of ribociclib is usually between 5 to 8 months [12]. Distribution of lesions is more commonly seen in the sun exposed areas (face, hand, and feet). Treatments used were topical emollients, topical steroids, topical calcineurin inhibitors and systemic steroids. Despite above treatment options, minimal therapeutic results were observed. Awareness among physicians regarding this dermatological side effect is necessary to ensure proper patient counselling and for management of the toxicity. More research is required to explain causal association, to determine risk factors and for potential therapeutic strategies. It can be determined as class specific side effect.

Conclusion

Vitiligo is a rare side effect seen with the CDK4/6 inhibitor Ribociclib. Since vitiligo is still a social stigma, understanding the incidence rates of therapy induced vitiligo, clinicians can enhance patients' adherence to the drug and optimize patient outcomes. Risks and benefits of the drug must be explained to the family in detail and shared decision making with family is needed for continuation of the drug. Further research is required to understand risk factors, incidence, and treatment strategies for ribociclib induced dermatological side effects.

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