# Osimertinib-associated ashy dermatosis–like hyperpigmentation

Pattamon Lertpichitkul, MD, Jade Wititsuwannakul, MD, Pravit Asawanonda, MD, DSc, and Pawinee Rerknimitr, MD, MSc
*Bangkok, Thailand*

***Key words:*** ashy; epidermal growth factor receptor inhibitor; hyperpigmentation; osimertinib; rash.

## INTRODUCTION

Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI). It is approved for patients with advanced non–small-cell lung cancer who have disease progression despite the administration of the first- or second-generation EGFR-TKI by acquiring a second mutation in exon 20 of the EGFR T790M.[1]

EGFR plays a pivotal role in maintaining skin homeostasis. Therefore, dermatologic adverse events (dAEs) commonly occur during the course of EFGR-TKI therapy that specifically inhibits this pathway. Common manifestations include papulopustular eruptions, pruritus, paronychia, hair changes, and xerosis. However, pigmentary changes in association with EGFR-TKI treatment are rarely reported.[2] Here, we describe an unusual case of slate gray hyperpigmentation associated with osimertinib therapy.

*Abbreviations used:*

| | |
|---|---|
| AD: | ashy dermatosis |
| dAE: | dermatologic adverse event |
| EGFR: | epidermal growth factor receptor |
| TKI: | tyrosine kinase inhibitor |

## CASE REPORT

A 71-year-old woman presented with a complaint of skin darkening. Three years before this visit, she received a diagnosis of non–small-cell lung cancer (stage T3, N2, M0) with a positive EGFR mutation (L858R). She underwent a lobectomy and the neoadjuvant erlotinib was started. However, she initially refused to continue erlotinib due to mucositis. After 9 months of surveillance, multiple brain and lymph node metastases developed. She was then treated with whole-body radiation therapy with stereotactic surgery, and erlotinib therapy was reintroduced. The disease responded well to a 150-mg daily dosage of erlotinib. She experienced adverse events including mild diarrhea, acneiform eruption, pruritus, paronychia, and skin dryness during the course of therapy; however, these adverse effects were well controlled and tolerable during this time. In the eighth month of erlotinib treatment, a computed tomography scan showed bone metastases in the ribs and vertebrae. Erlotinib treatment was replaced by osimertinib 80 mg daily, although molecular profiling results were positive for EGFR mutation without T790M mutation. Fortunately, osimertinib effectively stopped the progression of metastases.

Approximately 6 months into the osimertinib treatment, the patient noticed progressive skin darkening all over her body without any associated symptoms. She confirmed that she had no redness or inflammatory rashes preceding the dark spots. She had, however, experienced dry skin and pruritus since her erlotinib treatment and remarked that these symptoms had persisted. Apart from the cancer treatments, her medication history included 10 years of amlodipine for hypertension and 2 years of vitamin E, folic acid, and iron supplements. No new topical agents were introduced before or during this period.

From the Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Skin and Allergy Research Unit, Chulalongkorn University, Bangkok.

Funding sources: None.
Conflicts of interest: None disclosed.

Correspondence to: Pawinee Rerknimitr, MD, MSc, Division of Dermatology, Department of Medicine, Faculty of Medicine, Skin and Allergy Research Unit, Chulalongkorn University, 1873 Rama IV Rd, Pathumwan, Bangkok 10330, Thailand. E-mail: pawinee.r@chula.ac.th.

JAAD Case Reports 2020;6:86-8.
2352-5126



https://doi.org/10.1016/j.jdcr.2019.11.008

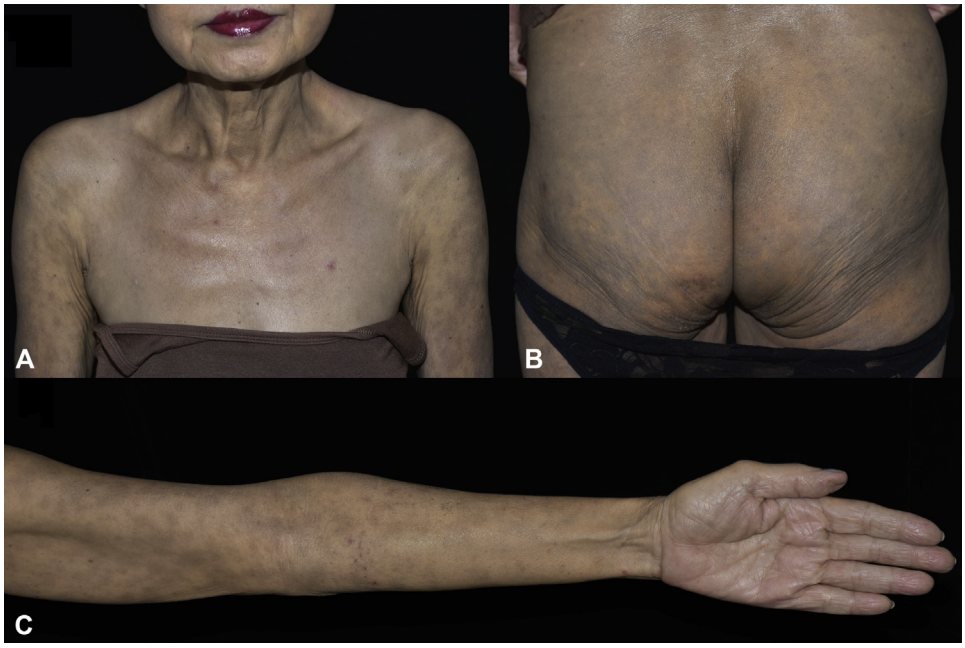


**Fig 1.** Generalized slate gray, hyperpigmented patches were found on (**A**) the chest, (**B**) the buttocks, and (**C**) both forearms.

Physical examination showed generalized skin dryness with excoriation. Symmetric discrete ill-defined small and large slate gray hyperpigmented macules and patches on the forehead, upper portion of the back, abdomen, and both forearms and legs were observed. Some of the lesions were confluent, covering the large areas of the body. These lesions were detected both on sun-protected and -exposed areas (Fig 1). Hypertrichosis on the face and trichomegaly of the eyelashes were also found. Laboratory results were unremarkable. A punch biopsy specimen from forearm showed prominent pigmentary incontinence in the upper dermis. Subtle vacuolar alteration was noted at the overlying epidermis, and necrotic keratinocytes were not seen (Fig 2). The histopathologic findings are compatible with ashy dermatosis (AD).

Except for pigmentary lesions, xerosis, and mild pruritus, the patient had no associated symptoms. Osimertinib was a crucially needed therapy, so no additional treatment or drug discontinuation was attempted. The condition has remained stable since.

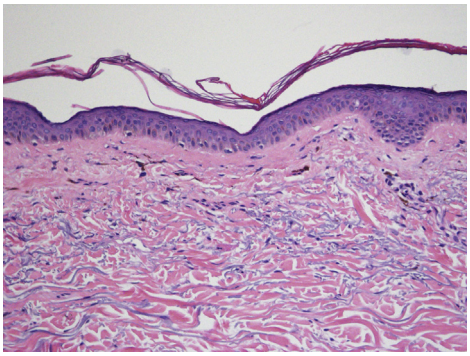

**Fig 2.** Hematoxylin-eosin stain shows pigmentary incontinence in the upper dermis and vacuolar degeneration at the dermoepidermal junction. (Original magnification: ×100.)

## DISCUSSION

EGFR-TKIs are used effectively as a treatment for metastatic non—small-cell lung cancer with EGFR mutation.[1,3] First- and second-generation drugs include gefitinib, erlotinib, and afatinib. Although all have favorable efficacies, each agent differs in its affinity to EGFR. Correspondingly, this leads to different incidences of dAEs and tolerability profiles.[1] The wild-type EGFR is typically found in the epidermis, outer root sheath of the hair follicles, epithelium of sweat and sebaceous glands, and nail apparatus.[1] Osimertinib exhibits a potent selective inhibitory activity against T790M mutant while sparing the wild-type EGFR. Thus, it is associated with fewer dAEs compared with earlier-generation drugs.[3,4] Unlike immune checkpoint inhibitors (anti—PD-1/PD-L1), EGFR-TKIs are rarely associated with lichenoid dermatitis.[5]

Pigmentary changes caused by EGFR-TKIs are unusual. Only 2 cases have been reported to date,[6] and both were induced by gefitinib and thought to be due to postinflammatory hyperpigmentation.

Both manifested as progressively multifocal hyperpigmented patches that developed after several months of gefitinib administration. Pigmentation occurred after severe acneiform eruptions.[6] In the current case, the ashy discolored macules did not arise on the previously inflamed skin but, rather, appeared de novo. Therefore, the process of post-inflammatory hyperpigmentation is unlikely.

The slate gray hyperpigmented patches found in our patient both clinically and pathologically resembled those of AD. AD is an idiopathic acquired skin condition with a clinical presentation of slowly progressive, dark bluish to slate gray, hyperpigmented macules that can coalesce into patches. Lesions are symmetrically located on the face, neck, trunk, and upper limbs.[7] The etiology and pathogenesis are still unknown. Established predisposing factors include ingestion of oral contrast media, ethambutol, fluoxetine, chlorothalonil, and proton-pump inhibitors.[7,8] In addition, the AD disease spectrum has been reported to be associated with intestinal parasitism, enteroviral, hepatitis C, and HIV infections.[8] Although AD may arise without provocative agents, our patient experienced pigmentary changes after starting osimertinib treatment for 6 months. This time interval is compatible with the reported drug-induced AD latency period of 2 to 12 months.[9] Because of its asymptomatic nature, cosmesis is the primary concern in patients affected by AD. In adults, lesions tend to persist, and no criterion standard treatment is currently available.[10]

In summary, we report an undescribed case of AD-like hyperpigmentation associated with osimertinib therapy. In addition to the classic EGFR-TKI–related dAEs, this case highlights a possible adverse skin reaction associated with osimertinib use.

The authors graciously thank the Skin and Allergy Research Unit, Chulalongkorn University, for their support and Professor Virote Sriuranpong, medical oncologist, who cares for this patient.

## REFERENCES

1. Chu CY, Choi J, Eaby-Sandy B, Langer CJ, Lacouture ME. Osimertinib: a novel dermatologic adverse event profile in patients with lung cancer. *Oncologist*. 2018;23:891-899.
2. Dai J, Belum VR, Wu S, Sibaud V, Lacouture ME. Pigmentary changes in patients treated with targeted anticancer agents: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77:902-910.
3. Yi L, Fan J, Qian R, Luo P, Zhang J. Efficacy and safety of osimertinib in treating EGFR-mutated advanced NSCLC: a meta-analysis. *Int J Cancer*. 2019;145:284-294.
4. Lamb YN, Scott LJ. Osimertinib: a review in T790M-positive advanced non-small cell lung cancer. *Target Oncol*. 2017;12:555-562.
5. Pugliese SB, Neal JW, Kwong BY. Management of dermatologic complications of lung cancer therapies. *Curr Treat Options Oncol*. 2015;16:50.
6. Chang G-C, Yang T-Y, Chen K-C, Yin M-C, Wang R-C, Lin Y-C. Complications of therapy in cancer patients. *J Clin Oncol*. 2004;22:4646-4648.
7. Nguyen K, Khachemoune A. Ashy dermatosis: a review. *Dermatol Online J*. 2019;25. pii: 13030/qt44f462s8.
8. Kumarasinghe SPW, Pandya A, Chandran V, et al. A global consensus statement on ashy dermatosis, erythema dyschromicum perstans, lichen planus pigmentosus, idiopathic eruptive macular pigmentation, and Riehl's melanosis. *Int J Dermatol*. 2019;58:263-272.
9. Chang H-C, Chang Y-S, Wang K-H, Cheng T, Tsai H-H. Esomeprazole-induced ashy dermatosis-like drug eruptions. *Australas J Dermatol*. 2019;60:e232-e233.
10. Wu A, Vaidya S. Literature review of treatment outcomes for lichen planus pigmentosus, erythema dyschromicum perstans, and ashy dermatosis. *J Cutan Med Surg*. 2018;22:643-645.