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Reversal of Cushing Pigmentation by Sunitinib

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A 53-year-old woman with ectopic Cushing syndrome presented with progressive skin pigmentation. Two years earlier, she had presented to a local hospital complaining of muscle weakness, lower extremity edema, and hypertension. She had been diagnosed as ACTH-dependent Cushing syndrome and referred to our hospital for further investigation. Although no pituitary tumor was detected by MRI, a pancreatic tumor was detected by a contrast-enhanced CT scan, and the tumor was surgically resected. Pathological examination confirmed an ectopic ACTH-producing pancreatic neuroendocrine tumor based on positive immunostaining for ACTH and chromogranin A.

Postoperatively, a decrease in the plasma ACTH (from 349.0 pg/mL to 14.4 pg/mL; normal range 7.2 to 63.3 pg/mL) was observed. One year after surgery, however, liver metastases developed, and plasma ACTH began to increase, which was not suppressed by administration of octreotide, everolimus, and streptozotocin. Two years after surgery, the patient's plasma ACTH exceeded 5000 pg/mL, and she complained of progressive skin pigmentation (Fig. 1a and 1b). Administration of sunitinib, an inhibitor of multiple tyrosine kinases, was then initiated. After 6 weeks, sunitinib dramatically improved skin pigmentation (Fig. 1c and 1d), although it did not suppress plasma ACTH or tumor progression.

Skin pigmentation is a classical sign of ACTH-dependent Cushing syndrome. It is believed that the melanocortin 1 receptor on melanocytes plays a major role in ACTH-induced pigmentation [1, 2]. However, analyses of so-called "white Addison" cases suggest that there are additional pathways that are also involved in ACTH-induced pigmentation [2–4].

In the current case, skin pigmentation was almost completely reversed by sunitinib without successful suppression of plasma ACTH and tumor progression. A previous report showed that sunitinib may cause hair depigmentation in a patient without Cushing syndrome [5]. In line with this, several tyrosine kinase inhibitors are also reported to be associated with skin or hair depigmentation [6]. Therefore, although depigmentation is a known adverse effect of sunitinib in patients without Cushing syndrome, the importance of this finding is that ACTH-dependent skin pigmentation in Cushing syndrome is also sensitive to sunitinib. We speculate that a sunitinib-sensitive kinase, such as c-Kit [7], is involved in the ACTH-induced pigmentation pathway.

In conclusion, the current case suggests that ACTH-induced pigmentation can be reversed by sunitinib.

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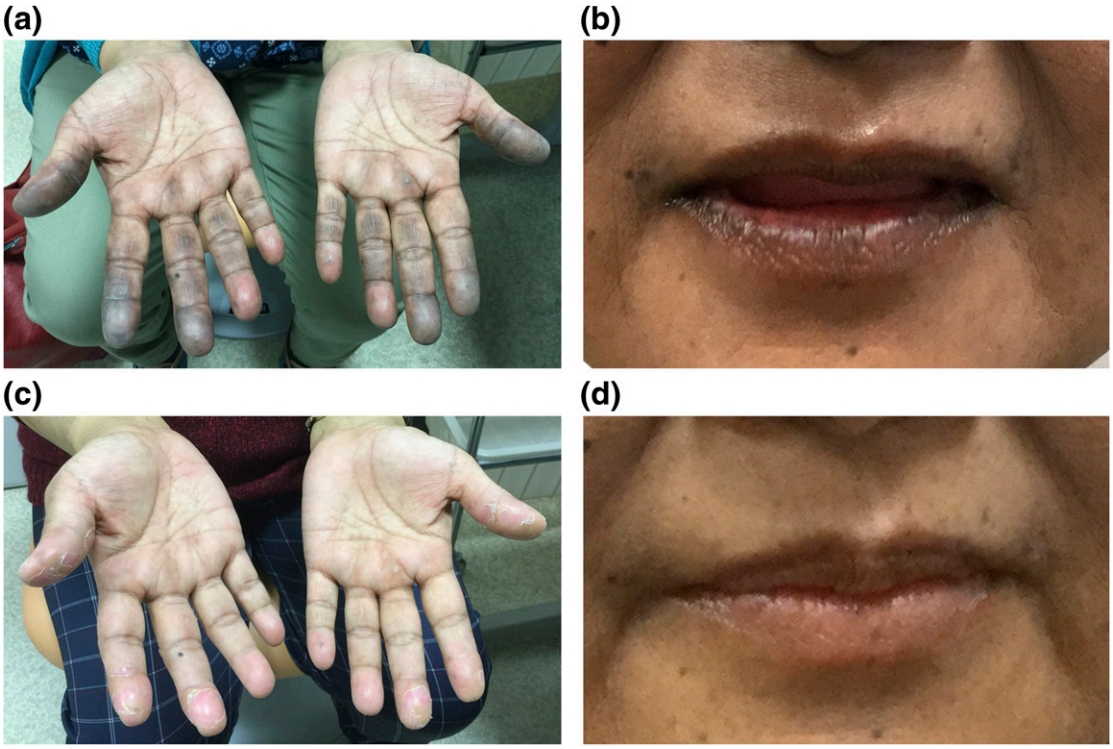

Figure 1. Skin pigmentation of (a) hands and (b) lips before sunitinib administration. (c) Hands and (d) lips after 6 wk of sunitinib treatment.

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References and Notes

1. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;**445**(7130):843–850.
2. Stratakis CA. "Patients can have as many gene variants as they damn well please": why contemporary genetics presents us daily with a version of Hickam's dictum. *J Clin Endocrinol Metab*. 2012;**97**(5): E802–E804.
3. Kendereski A, Micić D, Sumarac M, Zorić S, Macut D, Colić M, Skaro-Milić A, Bogdanović Z. White Addison's disease: what is the possible cause? *J Endocrinol Invest*. 1999;**22**(5):395–400.
4. Turan S, Hughes C, Atay Z, Guran T, Haliloglu B, Clark AJ, Bereket A, Metherell LA. An atypical case of familial glucocorticoid deficiency without pigmentation caused by coexistent homozygous mutations in MC2R (T152K) and MC1R (R160W). *J Clin Endocrinol Metab*. 2012;**97**(5):E771–E774.
5. Brzezniak C, Szabo E. Images in clinical medicine. Sunitinib-associated hair depigmentation. *N Engl J Med*. 2014;**370**(17):e27.
6. Zuo RC, Apolo AB, DiGiovanna JJ, Parnes HL, Keen CM, Nanda S, Dahut WL, Cowen EW. Cutaneous adverse effects associated with the tyrosine-kinase inhibitor cabozantinib. *JAMA Dermatol*. 2015; **151**(2):170–177.
7. Robert C, Soria JC, Spatz A, Le Cesne A, Malka D, Pautier P, Wechsler J, Lhomme C, Escudier B, Boige V, Armand JP, Le Chevalier T. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;**6**(7):491–500.