Azusa Sano, MD
Department of General Medicine, National Defense Medical College, Saitama, Japan

Yosuke Ono, MD, PhD
Department of General Medicine, National Defense Medical College, Saitama, Japan

Naoya Fujita, MD
Department of General Medicine, National Defense Medical College, Saitama, Japan

Yuji Tanaka, MD, PhD
Department of General Medicine, National Defense Medical College, Saitama, Japan

Spotty skin pigmentation in Carney complex

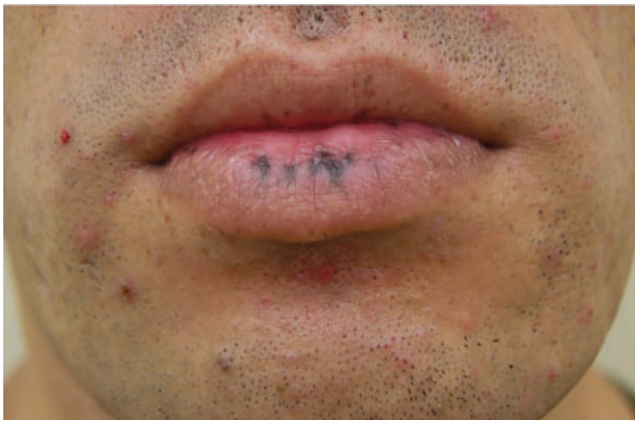

Figure 1. Spotty skin pigmentation on the lower lip. Also, the lips were thick and coarse, consistent with acromegaly.

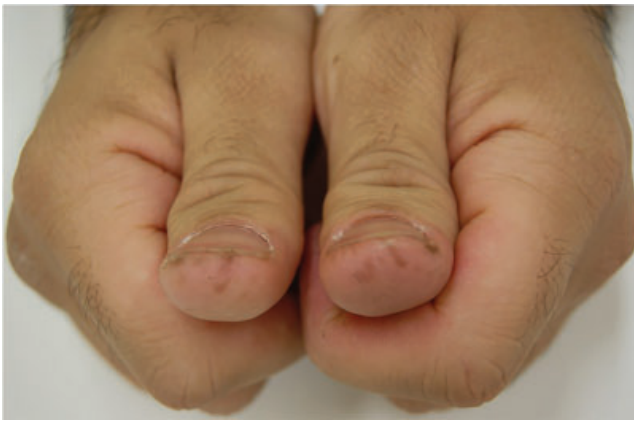

Figure 2. Pigmentation on the tips of the thumbs. The patient's hands were noted to be large in size, consistent with acromegaly.

A 33-year-old man with a known history of Carney complex presented to our hospital. At 18 years of age, he was diagnosed with adrenal Cushing syndrome and acromegaly, for which he had undergone bilateral adrenalectomy and transsphenoidal surgery. Pathological examination revealed primary pigmented nodular adrenocortical disease at that time.

On examination, spotty skin pigmentation was observed on the lower lip (**Figure 1**) and both thumb tips (**Figure 2**). Moreover, the patient's lips were noted to be thick and coarse and his hands were large in size, consistent with acromegaly. Four of his family members had similar areas of pigmentation.

DIFFERENTIAL DIAGNOSIS OF SPOTTY SKIN PIGMENTATION

Physicians commonly encounter patients with facial pigmented macules in daily practice, and this may provide an important clue for diagnosing underlying systemic disease. It should be determined if the patient has other areas of skin pigmentation and if the lesions are congenital or acquired.

In particular, characteristic skin findings and their locations can indicate underlying hereditary lentiginosis syndromes including Peutz-Jeghers syndrome, Carney complex, Noonan syndrome with multiple lentigines, Bannayan-Riley-Ruvalcaba syndrome, and Laugier-Hunziker syndrome.[1,2] Among these syndromes, differentiating between Peutz-Jeghers syndrome and Carney complex is clinically important because of similar densities and distributions of lentigines. Patients with Peutz-Jeghers syndrome typically have brown-blue macules found on the lips and oral mucosa, eyes, nares, palms, soles, and perianal region.[3] In contrast, patients with Carney complex typically have brown-to-black macules that are mostly found on the lips, eyelids, or canthi, and less frequently on genital mucosa or fingers.[4] To assist in differential diagnosis between Peutz-Jeghers syndrome and Carney complex, it is important to note that lentigines are not usually observed on the oral mucosa in Carney complex.[4] In addition, thick and coarse lips and large-sized hands are indications of acromegaly associated with Carney complex.

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CARNEY COMPLEX

Carney complex is rare, hereditary in 50% of patients.[1] In a large case series, 63% were female and 37% were male.[5] Approximately 80% of patients have spotty skin pigmentation,[6] with lentigines that usually appear before puberty and increase in number and density during and after adolescence.[1] Pigment intensity tends to decrease gradually with advancing age, but lentigines can still be observed in the elderly.[1] Lentigines in genital areas that have not been exposed to sunlight provide important information to diagnose Carney complex.[4]

Mechanisms of skin pigmentation in Carney complex remain unclear. Carney complex is caused by mutations in the protein kinase cyclic adenosine monophosphate (cAMP)-dependent type I regulatory subunit alpha (*PRKAR1A*) gene, and loss of *PRKAR1A* function leads to increased cAMP activity.[1,7] In general, pigmentation is regulated by the cAMP signaling pathway.[4] Therefore, the skin pigmentation in Carney complex is probably caused by cAMP pathway activation.[4]

Hyperpigmentation in Cushing disease

Some patients with pituitary Cushing disease or ectopic adrenocorticotropic hormone (ACTH) syndrome may have generalized hyperpigmentation of the skin and oral mucosa, caused by increased ACTH that acts through binding to melanocyte-stimulating hormone receptors.[8] Hyperpigmentation does not occur in patients with adrenal Cushing syndrome because overproduction of cortisol suppresses ACTH secretion.[8]

PATIENT'S TREATMENT

This patient received treatment with cabergoline and octreotide, but blood tests revealed high serum levels of growth hormone and insulin-like growth factor 1. After altering treatment to pegvisomant, at 18-month follow-up, the patient's serum concentration of insulin-like growth factor 1 had normalized, but the pigmented lesions remained unchanged. The patient declined genetic testing.

CONCLUSION

Recognition of characteristic skin findings associated with familial lentiginosis syndromes is key for early diagnosis and can lead to early detection and treatment of multiple endocrine tumors and life-threatening cardiac myxomas, and thereby curtail disease-specific mortality.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: *Yosuke Ono, Department of General Medicine, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513 Japan; onoyousuke1979@yahoo.co.jp*