JOURNAL OF
CUTANEOUS IMMUNOLOGY
AND ALLERGY

TYPE Letter to the Editor
PUBLISHED 28 August 2026
DOI 10.3389/jcia.2026.17110

OPEN ACCESS

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RECEIVED 09 June 2026
REVISED 31 July 2026
ACCEPTED 11 August 2026
PUBLISHED 28 August 2026

CITATION
Fujiwara M, Iida T, Oda A, Takeshita H, Namiki T and Okiyama N (2026) Asymmetrical anhidrosis with hyperpigmentation in a patient with type 1 diabetes.
J. Cutan. Immunol. Allergy 9:17110.
doi: 10.3389/jcia.2026.17110

Asymmetrical anhidrosis with hyperpigmentation in a patient with type 1 diabetes

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KEYWORDS
anhidrosis, hyperpigmentation, melanocyte, sweating, type 1 diabetes

Dear Editors,

Typically, the unaffected areas in patients with asymmetrical sweating disorders, such as Harlequin syndrome, show no skin abnormalities other than temporary hyperemia. Additionally, reductions in sweating associated with diabetes usually occur symmetrically on the distal extremities [1]. Here, we present the case of a patient with type 1 diabetes who had asymmetrical anhidrosis characterized by hyperpigmentation in areas where the sweating function remained intact.

A 48-year-old Japanese man first noticed a reduction in sweating in his palms and soles 6 years before presentation. Over time, the area of impaired sweating spread to his trunk, and he noticed the gradual development of hyperpigmentation in areas where sweating persisted. He had been diagnosed with type 1 diabetes 2 years earlier, and the condition was suspected to be the acute-onset type because high blood glucose concentrations had not been identified in previous annual medical checkups. Although he had been receiving insulin treatment since the diagnosis, his diabetes was not well controlled when he presented at our hospital with an HbA1c level of 8.9%. He visited the hospital because of heat intolerance, and he was noted to have diffuse hyperpigmentation on his left shoulder, right chest and abdomen, and right back (Figures 1A,B). The pigmentation was particularly pronounced in the area between his right armpit and right back.

A thermal sweating test using Minor's method (the iodine–starch test; Figures 1C,D) and thermography (Figures 1E,F) revealed that the areas of hyperpigmentation largely corresponded to the areas where sweating function remained. Anhidrotic areas were detected on the right shoulder, the left side of the chest and abdomen, and the entire left and right lower back of the patient. The quantitative sudomotor reflex test was performed on his back and revealed that sweat production in response to acetylcholine stimulation was lower on the left than on the right side (left back: 0.049 mg/cm^2/min; right back: 0.159 mg/cm^2/min). Magnetic resonance imaging of his brainstem and spine revealed no abnormalities. In addition, ^{123}I-meta-iodobenzylguanidine myocardial scintigraphy did not reveal any impairment of sympathetic nerve function in the heart. No orthostatic hypotension was identified during the active standing test, and no pupillary abnormalities were found. A neurological examination revealed no sensory or motor neuropathy, only a widespread impairment of sweating. Anti-nuclear and anti-Sjögren's syndrome type A and B antibodies were not detected.

Skin biopsies were performed on the right side of the patient's back, where sweating function was normal and hyperpigmentation was present, and on the left side of his back, where sweating was impaired. The eccrine glands in the areas with impaired sweating were slightly atrophied compared with those in the unaffected areas (Figures 1G,H). Immunohistochemical staining for tubulin β3 revealed a reduction in the number of nerve fibers around the sweat glands in the areas where sweating was impaired (Figures

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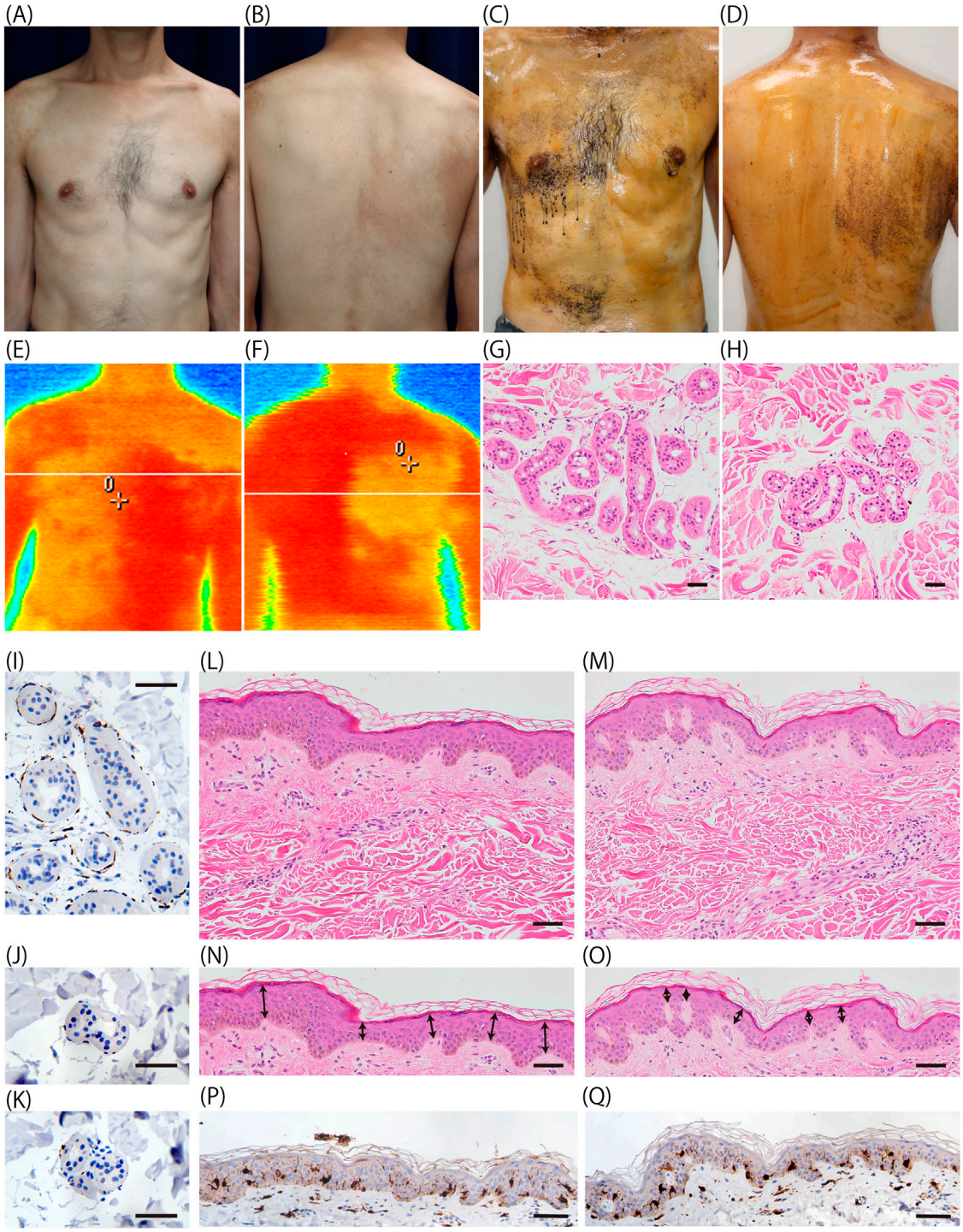

FIGURE 1
Pigmentation of areas of skin unaffected by asymmetrical anhidrosis. **(A,B)** The skin of the patient's anterior **(A)** and posterior trunk **(B)**. The patient had hyperpigmentation on his left shoulder, right chest and abdomen, and right upper back. **(C–F)** The results of the thermal sweating test using Minor's method (C, anterior; D, posterior) and thermography (E, anterior; F, posterior). Areas that stained black using Minor's method **(C,D)** and areas that appeared to have a low temperature on thermography **(E,F)** indicated intact sweating. The areas of pigmentation **(A, B)** and sweating **(C–F)** largely coincided. **(G,H)** Hematoxylin and eosin (HE)-stained skin sections, showing the eccrine glands in the patient's right back, where sweating occurred **(G)**, and in his left back, where it did not **(H)**. The glands in the areas where no sweating was observed were slightly atrophied **(H)** compared with those in the areas where sweating was observed **(G)**. **(I–K)** Immunohistochemistry for tubulin β3 (BioLegend antibody #801213) in the skin of the right **(I)** and left **(J,K)** sides of the patient's back. **(L,M)** HE images of the epidermis and dermis in the right **(L)** and the left (M) back. In the right back **(L)**, where sweating was observed, there was slightly more pigmentation in the basal layer of the epidermis and a slight thickening of the epidermis compared with the findings in the left back **(M)**. In addition, the collagen fibers in the dermis of the right back **(L)** tended to be slightly thicker than those of the left back **(M)**. **(N,O)** Thickness of the epidermis, measured at the five thinnest points between the rete ridges, as indicated by the double-headed arrows in the skin sections from the right **(N)** and left **(O)** sides of the patient's back. **(P,Q)** Immunohistochemistry for S100 (Abcam antibody #4066) in skin sections of the right **(P)** and left **(Q)** sides of the patient's back. Scale bars: 20 μm **(G)**, 50 μm **(L)**.

1I–K). In contrast, the basal layer of the epidermis in the areas where sweating function remained exhibited greater keratinocyte pigmentation (Figures 1L,M), accompanied by slight epidermal thickening (epidermal thickness, excluding the stratum corneum and measured between the rete ridges: 52.8 ± 12.1 μm in the sweating areas; 31.1 ± 6.7 μm in the non-sweating areas [mean ± standard deviation]; Figures 1N,O). In addition, collagen fibers in the dermis were slightly thicker in the areas where sweating function remained. There were no notable differences in the number of melanocytes in the epidermis of the two areas (Figures 1P,Q).

Although hyperpigmentation of the unaffected areas is rarely observed in patients with asymmetrical anhidrosis, it has been reported in some patients with Ross syndrome, which is characterized by segmental anhidrosis in combination with areflexia and a tonic pupil [2]. The mechanism by which pigmentation develops in areas where the sweating function remains is unknown. In the present patient, because there was no apparent change in the number of melanocytes, it is likely that the difference in the amount of melanin deposition was the result of functional changes in the melanocytes. Differences in the skin environment, such as sweating, blood flow, temperature, and pH, may influence melanin production [3]. Examination of the patient's biopsy specimens indicated differences in the condition of keratinocytes and fibroblasts between the affected and unaffected areas, which could influence melanocyte function through secreted factors and cell-to-cell contacts [3]. Based on these findings, we presumed that the presence or absence of sweating altered the microenvironment of the melanocytes, affecting the signals they received from surrounding cells and altering melanin synthesis and deposition. Additionally, it has been reported that melanin loss in the skin of patients with type 1 diabetes is associated with the level of glycemic control and the presence or absence of neuropathy [4]. The present case suggests a possible connection between a neuropathy-associated reduction in sweating and hypopigmentation, which would have accentuated the hyperpigmentation in the sweating areas of the present patient.

Sweating dysfunction is a well-recognized complication of diabetes and may present with hyperhidrosis, gustatory sweating, and anhidrosis/hypohidrosis with variable distribution [1, 5]. Distal hypohidrosis associated with diabetic polyneuropathy is one of the most common patterns and is thought to result from hyperglycemia-induced damage to long peripheral axons [6]. In the present case, a loss of sweating initially occurred in the distal extremities and gradually spread to the trunk in an asymmetrical pattern. Although the patient's sweating impairment preceded the onset of diabetes, his heat intolerance worsened around the time of diabetes onset. The progressive expansion of areas with impaired sweating, as in the present patient, is occasionally observed in patients with segmental anhidrosis, including Ross syndrome [2]. Additionally, the extensive nature of the sweating dysfunction and the absence of peripheral neuropathy other than that related to sweating probably distinguishes the present patient from those with typical diabetes-related peripheral neuropathy. Based on the distribution of the anhidrotic areas, revealed by thermography, and the reduction in the number of nerve fibers around the sweat glands, it can be inferred that there may be loss of postganglionic fibers at the level of the sympathetic ganglion. Furthermore, Minor's method revealed heterogeneity in the volume of sweat produced within the areas where sweating persisted. This heterogeneity may be explained by variations in the number of nerves remaining within each sympathetic ganglion. However, because the distribution of sweating appears not to correspond precisely to the sympathetic segments, it cannot be excluded that sweat gland function is influenced by local skin conditions.

There is currently no established method for restoring sweating in patients with segmental or asymmetrical anhidrosis. For this patient, therefore, the treatment focused on preventing heat stroke [1]. Specifically, we advised him to take frequent breaks when in hot environments and when exercising, and to regularly apply a wet towel to help compensate for the lack of sweating.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies involving humans because this paper reports individual case. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MF and TI wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by MHLW Health and Labour Sciences Research Grant number 25FC1014.

Acknowledgments

We thank Chiyako Miyagishi for her technical assistance and Mark Cleasby, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

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